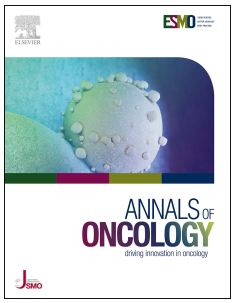


ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer†

A. Gennari, F. André, C.H. Barrios, J. Cortés, E. de Azambuja, A. DeMichele, R. Dent, D. Fenlon, J. Gligorov, S.A. Hurvitz, S.-A. Im, D. Krug, W.G. Kunz, S. Loi, F. Penault Lorca, J. Ricke, M. Robson, H.S. Rugo, C. Saura, P. Schmid, C.F. Singer, T. Spanic, S.M. Tolaney, N.C. Turner, G. Curigliano, S. Loibl, S. Paluch-Shimon, N. Harbeck, on behalf of the ESMO Guidelines Committee

PII: S0923-7534(21)04498-7

DOI: https://doi.org/10.1016/j.annonc.2021.09.019

Reference: ANNONC 766

To appear in: *Annals of Oncology*

Received Date: 28 September 2021

Accepted Date: 30 September 2021

Please cite this article as: Gennari A, André F, Barrios CH, Cortés J, de Azambuja E, DeMichele A, Dent R, Fenlon D, Gligorov J, Hurvitz SA, Im SA, Krug D, Kunz WG, Loi S, Lorca FP, Ricke J, Robson M, Rugo HS, Saura C, Schmid P, Singer CF, Spanic T, Tolaney SM, Turner NC, Curigliano G, Loibl S, Paluch-Shimon S, Harbeck N, on behalf of the ESMO Guidelines Committee, ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer†, *Annals of Oncology* (2021), doi: https://doi.org/10.1016/j.annonc.2021.09.019.

ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer†

A. Gennari[1], F. André[2], C. H. Barrios[3], J. Cortés[4-7], E. de Azambuja[8], A. DeMichele[9], R. Dent[10], D. Fenlon[11], J. Gligorov[12], S. A. Hurvitz[13,14], S.-A. Im[15], D. Krug[16], W. G. Kunz[17], S. Loi[18], F. Penault Lorca[19], J. Ricke[217], M. Robson[20], H. S. Rugo[21], C. Saura[22], P. Schmid[23], C. F. Singer[24], T. Spanic[25], S. M. Tolaney[26], N. C. Turner[27], G. Curigliano[28], S. Loibl[29], S. Paluch-Shimon[30], N. Harbeck[31], on behalf of the ESMO Guidelines Committee*

[1]Department of Translational Medicine, University of Piemonte Orientale, Novara, Italy; [2]Breast Cancer Unit, Medical Oncology Department, Gustave Roussy – Cancer Campus, Villejuif, France; [3]Oncology Research Center, Grupo Oncoclínicas, Porto Alegre, Brazil; [4]International Breast Cancer Center (IBCC), Quironsalud Group, Barcelona; [5]Scientific Department, Medica Scientia Innovation Research, Valencia; [6]Vall d'Hebron Institute of Oncology (VHIO), Barcelona; [7]Universidad Europea de Madrid, Faculty of Biomedical and Health Sciences, Department of Medicine, Madrid, Spain; [8]Medical Oncology Department, Institute Jules Bordet and l'Université Libre de Bruxelles (U.L.B.), Brussels, Belgium; [9]Hematology/Oncology Department, Hospital of the University of Pennsylvania, Philadelphia, USA; [10]Department of Medical Oncology, National Cancer Centre Singapore, Singapore; [11]College of Human and Health Sciences, Swansea University – Singleton Park Campus, Swansea, UK; [12]Department d' Oncologie Médicale, Institut Universitaire de Cancérologie AP-HP, Sorbonne Université, Hôpital Tenon, Paris, France; [13]Department of Medicine/Division of Hematology Oncology, David Geffen School of Medicine, University of California, Los Angeles; [14]Jonsson Comprehensive Cancer Center, Los Angeles, USA; [15]Department of Internal Medicine, Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea; [16]Department of Radiation Oncology, University Hospital Schleswig-Holstein – Campus Kiel, Kiel, Germany; [17]Department of Radiology, University Hospital, LMU Munich, Munich, Germany; [18]Peter MacCallum Cancer Centre, Melbourne, Australia; [19] Centre de Lutte Contre le Cancer Jean Perrin, Imagerie Moléculaire et Stratégies Théranostiques, Université Clermont Auvergne, UMR INSERM-UCA, Clermont Ferrand, France; [20]Medicine Department, Memorial Sloan Kettering Cancer Center, New York; [21] Department of Medicine,

University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, USA; [22]Breast Cancer Program, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [23]Centre of Experimental Cancer Medicine, Cancer Research UK Barts Centre, Barts and The London School of Medicine and Dentistry, London, UK; [24]Center for Breast Health and Department of Obstetrics & Gynecology, Medical University of Vienna, Vienna, Austria; [25]Europa Donna Slovenia, Slovenia; [26]Dana-Farber Cancer Institute, Boston, USA; [27]The Royal Marsden Hospital NHS Foundation Trust, London, UK; [28]Early Drug Development for Innovative Therapies Division, Istituto Europeo di Oncologia, IRCCS and University of Milano, Milan, Italy; [29]GBG Forschungs GmbH, Neu-Isenburg, Germany; [30]Sharett Institute of Oncology Department, Hadassah University Hospital & Faculty of Medicine Hebrew University, Jerusalem, Israel; [31]Breast Center, Department of Obstetrics & Gynecology and Comprehensive Cancer Center Munich, LMU University Hospital, Munich, Germany

**Correspondence to:* ESMO Guidelines Committee, ESMO Head Office, Via Ginevra 4, CH-6900 Lugano, Switzerland. E-mail: clinicalguidelines@esmo.org

†Approved by the ESMO Guidelines Committee: October 2012, last update September 2021. This publication supersedes the previously published version—Ann Oncol 2012;23(Suppl 7): vii11–vii19.

Running header: ESMO Clinical Practice Guidelines for metastatic breast cancer

Word count: 12,807 (excluding title page, acknowledgements, funding and disclosure sections); References: 94; Tables: 0; Figures: 6; Supplementary material: 1.

Key words:
Diagnosis, ESCAT, ESMO Clinical Practice Guideline, MCBS, metastatic breast cancer, treatment.

Highlights:

- This ESMO Clinical Practice Guideline provides key recommendations and algorithms for managing metastatic breast cancer.
- It covers diagnosis, staging, risk assessment, treatment, disease monitoring, palliative care and the patient perspective.
- ESMO-MCBS and ESCAT scores are given to describe the levels of evidence for treatment choices.
- The authors comprise an international expert group, with recommendations based on available evidence and expert opinion.
- In clinical practice, all recommendations provided need to be discussed with patients in a shared decision-making approach.

GENERAL PRINCIPLES

Metastatic breast cancer (MBC) is an incurable disease, but survival improvements have been reported with appropriate therapeutic strategies.[1-8] Systemic therapy is the standard of care in MBC but may be supplemented with locoregional treatments (LRTs) according to the disease status of the individual patient. Thus, a multidisciplinary team (MDT) is a prerequisite for optimal management. These guidelines are based on breast cancer (BC) biological subtypes even though modern targeted drugs may lead to revisions of these subtypes in the future, as exemplified by the first tumour-agnostic approvals.

Treatment decisions need to be made independent of patient age, but comorbidities and patient characteristics, as well as patient preferences, need to be considered as part of a shared decision-making process. In elderly patients, a comprehensive geriatric assessment may add important information.[9]

Supportive care should always be part of the treatment plan and early introduction of expert palliative care may help to better control symptoms.

Rechallenge with drugs previously used in the early breast cancer (EBC) setting is a reasonable option, provided that the disease-free interval (DFI) is ≥12 months after the last drug administration and that no remaining toxicities exist. Approved biosimilars can be used instead of originator drugs in all registered indications.[10]

This patient population should be encouraged to consider participation in clinical trials early in their disease course, with preference given to enrolment onto a clinical trial, if available, in each line of therapy.

INCIDENCE AND EPIDEMIOLOGY

With more than 400,000 cases in the European Union (EU) in 2018,[11] BC is the most frequent cancer affecting women. Although BC mortality in Europe has been declining over the last three decades,[12] there are still differences across various regions or countries. For women diagnosed with EBC, the 5-year survival probability is around 96% in Europe.[13] However, when MBC is diagnosed, the 5-year survival rate is in the range of 38%.[13] While BC survival rates have increased in recent years, there were still approximately 138,000 deaths from BC in Europe in 2018,[11] and in

terms of absolute numbers, MBC was still the leading cause of death from all cancers in women, accounting for ~3.6% of all deaths in women and 1.8% of all deaths in Europe in 2015.

MBC subsequent to therapy for EBC tends to have a more aggressive tumour biology and a worse outcome compared with *de novo* MBC.[14,15] In a retrospective cohort study covering the period 1990-2010,[14] *de novo* MBC incidence rates remained constant whereas subsequent MBC decreased. Yet, 5-year disease-specific survival (DSS) of *de novo* MBC improved over time from 28% to 55% whereas subsequent MBC worsened from 23% to 13%. Similar data were reported from the Munich Cancer Registry,[15] with improved survival for patients diagnosed with EBC over the past three decades likely attributable to modern (neo)adjuvant therapies. Over the same period, there has been an increase in liver and central nervous system (CNS) metastases and a decline in bone metastases. Thus, improvements in EBC therapies seem to have led to an alteration in tumour biology and metastasis presentation in subsequent MBC, presumably resulting from a molecular selection process.

Given the frequency of BC, the overall survival (OS) improvements observed and the fact that clinical presentation and tumour biology of MBC after EBC therapy have become more aggressive, optimal 'state of the art' management of MBC is essential to maintain and further improve outcomes of patients with MBC. Moreover, international guidelines may help to enable equality regarding the level of BC care, treatment options and outcomes across Europe and beyond.

DIAGNOSIS, PATHOLOGY AND MOLECULAR BIOLOGY

A proposed algorithm for the diagnostic work-up of MBC is shown in **Figure 1**. Patients with newly diagnosed or recurrent MBC should have a biopsy, if technically feasible, to confirm histology and to re-assess oestrogen receptor (ER), progesterone receptor (PgR) and human epidermal growth factor receptor 2 (HER2) status [I, B]. Biopsies of bone metastases should be avoided, whenever possible, due to technical limitations of biomarker detection in decalcified tissue. If there are important differences in ER/PgR and HER2 status between the primary tumour and recurrence, expert opinion and limited clinical trial evidence for HER2-targeted

therapies indicate that patients should be managed according to receptor status of the recurrent disease biopsy.[16] Nevertheless, this tumour heterogeneity needs to be taken into account for each new line of treatment and a re-biopsy may be appropriate in cases of mixed response.

In ER-low tumours (i.e. ER positive in 1%-9% tumour cells), limited evidence suggests that these cancers may be less sensitive to endocrine therapy (ET), although they may benefit from treatment with ET and CDK4/6 inhibitor combinations [IV, B].[17]

Further details of additional biomarkers that may guide the treatment approach in MBC can be found in the **supplementary text – section 1**, available at *Annals of Oncology* online.

Recommendations

- At first diagnosis of MBC, a biopsy should be performed to confirm histology and re-assess tumour biology (ER, PgR, HER2) [I, B].
- Other therapeutically-relevant biomarkers to be assessed as part of routine clinical practice include: germline BRCA1/2 mutation (*gBRCAm)* status in HER2-negative MBC, programmed death-ligand 1 (PD-L1) status in triple-negative breast cancer (TNBC) and *phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA)* in ER/PgR-positive, HER2-negative MBC [I, A; ESMO scale for clinical actionability of molecular targets (ESCAT) score: I-A].
- Genomic profiling and further diagnostic tests [e.g. on tumour tissue or circulating tumour DNA (ctDNA)] should only be performed as part of routine clinical practice if the result will change the treatment approach, as guided by the ESCAT scale, or if the patient can access appropriate clinical trials [V, B].

STAGING AND RISK ASSESSMENT

Recommendations

- The minimum imaging work-up for staging includes computed tomography (CT) of the chest and abdomen and bone scintigraphy [II, A].

- [18F]2-fluoro-2-deoxy-D-glucose (18F-FDG) positron emission tomography (PET)-CT may be used instead of CT and bone scans [II, B].[18,19]
- There is no evidence that any staging or monitoring approach provides an OS benefit over another.[19]
- The imaging modality chosen at baseline should be applied for disease monitoring to ensure comparability [III, C].
- The interval between imaging and treatment start should be ≤4 weeks.
- Evaluation of response should generally occur every 2-4 months depending on disease dynamics, location, extent of metastasis and type of treatment [V, B].[18]
- Disease monitoring intervals should not be shortened as there is no evidence of an OS benefit but potential for emotional and financial harm.[20] Less frequent monitoring is acceptable, particularly for indolent disease [IV, D].
- If progression is suspected, additional tests should be performed in a timely manner irrespective of planned intervals [V, B].[18]
- Repeat bone scans are a mainstay of evaluation for bone-only/predominant metastases, but image interpretation may be confounded by a possible flare during the first few months of treatment [III, C].[19]
- PET-CT might provide earlier guidance in monitoring bone-only/predominant metastases, but prospective trials are needed to study the impact on treatment decisions and OS [III, C].[19,21]
- Impending fracture risk should be evaluated by CT or X-rays. The spine instability neoplastic score provides reproducible risk assessment for vertebral metastases.[22] In case of suspected cord compression, magnetic resonance imaging (MRI) is the modality of choice [I, A].
- Brain imaging should not be routinely performed in all asymptomatic patients at initial MBC diagnosis or during disease monitoring. Patients with asymptomatic HER2-positive BC or TNBC have higher rates of brain metastases (BMs) at initial MBC diagnosis, even as the first site of recurrence. This may warrant subtype-oriented brain imaging in asymptomatic patients with MBC if detection of CNS metastases will alter the choice of systemic therapy [V, C]. Randomised trials to determine risks and benefits of brain screening are still underway (NCT03881605).[23]

- Symptomatic patients should always undergo brain imaging, preferably with MRI [II, D].

MANAGEMENT OF ADVANCED AND METASTATIC DISEASE

Luminal breast cancer

A proposed treatment algorithm for the management of hormone receptor (HR)-positive, HER2-negative MBC is shown in **Figure 2**.

Premenopausal women may be treated as postmenopausal providing that they have ovarian function suppression (OFS) or ovarian ablation. Bilateral oophorectomy provides more rapid oestrogen suppression than gonadotropin-releasing hormone agonists, the latter of which can cause a tumour flare in the first 2 weeks of treatment due to a short-term increase in hormone levels. Bilateral oophorectomy maybe preferable if a rapid response is required.

Primary endocrine resistance is considered for patients that relapse during the first 2 years of adjuvant ET or progression of disease (PD) within the first 6 months of first-line ET for MBC. Secondary (acquired) resistance is defined as relapse during adjuvant ET but after the first 2 years, relapse within 12 months of completing adjuvant ET or PD 6 months after initiating ET MBC.[24]

First-line treatment. CDK4/6 inhibitors combined with ET are the standard of care for ER-positive, HER2-negative MBC, with improved progression-free survival (PFS) and OS and a good toxicity profile seen in several trials [I, A; ESMO-Magnitude of Clinical Benefit (MCBS) v1.1 scores: 3-5].[25-31] ET plus CDK4/6 inhibition yields similar or better efficacy versus chemotherapy (ChT)[32,33] and is associated with less toxicity, making it the preferred treatment unless a patient has imminent organ failure. Although there is little data on use of CDK4/6 inhibitors after progression on CDK4/6 inhibitors, rechallenge may be possible after a treatment-free interval of ≥12 months based on evidence regarding rechallenge with other therapies.

CDK4/6 inhibitors are effective in *de novo* or recurrent MBC, in cases of primary or secondary endocrine resistance, in postmenopausal or premenopausal women [the latter with a luteinising hormone releasing hormone (LHRH) agonist] and in men (with an LHRH agonist). For patients who did not relapse on an aromatase inhibitor (AI), or within 12 months of stopping adjuvant AI, a CDK4/6 inhibitor in

combination with an AI is advised, with no clear advantage of fulvestrant seen in a phase II study.[34] In patients who relapsed on adjuvant AI therapy, or within 12 months of stopping adjuvant AI, a CDK4/6 inhibitor in combination with fulvestrant is advised [ESMO-MCBS v1.1 score: 4]. While there have been no head-to-head comparisons of the three approved CDK4/6 inhibitors, the efficacy of the three drugs in the metastatic setting appears similar. Palbociclib and ribociclib have not demonstrated single-agent efficacy and must be combined with ET; however, abemaciclib has demonstrated limited single-agent efficacy [ESMO-MCBS v1.1 score: 3].[35] Direct cross-trial comparisons are not possible due to the heterogeneous inclusion criteria. The toxicity profiles of these three drugs are slightly different,[25-30] and patients who develop severe toxicity characteristic of one CDK4/6 inhibitor may switch to a different CDK4/6 inhibitor.

ET alone in the first-line setting should be reserved for the small group of patients with comorbidities or a performance status (PS) that prevents the use of CDK4/6 inhibitor combinations; there are no clinical or biomarker data that can help to identify patients suitable for ET alone. Older age alone should not be used to select for endocrine monotherapy, although there may be a higher incidence of haematological adverse events (AEs) from CDK4/6 inhibitor therapy in older patients.[1]

In patients who required first-line ChT due to imminent organ failure, or who did not have access to a CDK4/6 inhibitor in the first-line setting, it is clinically acceptable to use ET plus a CDK4/6 inhibitor as a subsequent therapy.

Second-line treatment.

Options after progression on a CDK4/6 inhibitor. In patients who relapse after ET plus a CDK4/6 inhibitor, determination of somatic *PIK3CA* and *oestrogen receptor 1 (ESR1)* mutations (optional, if further AI is being considered), as well as germline *BRCA1/2* and *partner and localiser of BRCA2 (PALB2)* mutations (optional), is recommended.

The optimal sequence of endocrine-based therapy is uncertain after progression on CDK4/6 inhibitors. It is dependent on which agents were used previously [in the (neo)adjuvant or advanced settings], duration of response to

previous ET (for use of second-line single-agent ET), disease burden, patient preference and treatment availability. Evidence-based available options for second-line therapy include fulvestrant/alpelisib (for *PIK3CA*-mutated tumours) [I, B; ESMO-MCBS v1.1 score: 2; ESCAT score: I-A], exemestane /everolimus [[I, B; ESMO-MCBS v1.1 score: 2], tamoxifen/everolimus [II, B; off label], fulvestrant/everolimus [II, B; off label], AI, tamoxifen, fulvestrant, ChT or poly (ADP-ribose) polymerase (PARP) inhibitors for tumours harbouring *gBRCAm* [I, B; ESMO-MCBS v1.1 score: 4; ESCAT score: I-A].

The SOLAR-1 phase III randomised, placebo-controlled trial evaluated the role of alpelisib, an oral inhibitor of the phosphoinositide 3-kinase-alpha (PI3Kα) isoform, in combination with fulvestrant, for postmenopausal women and men who had been previously treated with an AI. In the *PIK3CA*-mutant cohort, alpelisib provided a PFS benefit of 11.0 months versus 5.7 months [hazard ratio (HR) for progression or death 0.65; 95% confidence interval (CI) 0.50-0.85; $P < 0.001$);[36] the median OS was 39.3 months for alpelisib/fulvestrant and 31.4 months for placebo/fulvestrant (HR 0.86; $P = 0.15$).[37] Toxicity was increased substantially in the alpelisib arm, especially hyperglycaemia, rash, gastrointestinal (GI) toxicity (nausea, vomiting, loss of appetite, mucositis, diarrhoea) and fatigue, which led to dose reductions/interruptions in ~70% and discontinuations in 25% of patients[36] although no new safety signals were observed with longer follow-up.[37] In view of the balance between efficacy and toxicity, it is crucial to carefully select candidates for this treatment, considering comorbidities, especially pre-existing diabetes and baseline glycated haemoglobin (HbA1c) levels. Hyperglycaemia from alpelisib occurs early and can be challenging to manage; collaboration with diabetes specialists is therefore recommended. It is also recommended that patients take non-sedating antihistamines to prevent rash at the start of therapy (see **supplementary Table S2,** available at *Annals of Oncology* online);[38] these can be discontinued after 4-8 weeks as the risk for rash is primarily in the first 2 weeks of therapy.

In view of the better efficacy/toxicity profile provided by CDK4/6 inhibitors, alpelisib plus ET should be used after a CDK4/6 inhibitor plus ET therapy. Although only 7% (20 patients) of SOLAR-1 patients had been previously exposed to a CDK4/6 inhibitor, the phase II trial, BYLieve, has shown efficacy of alpelisib with ET (AI or fulvestrant) after CDK4/6 inhibitor use.[38]

In the phase III BOLERO-2 trial, everolimus/exemestane significantly improved median PFS versus placebo/exemestane (7.8 versus 3.2 months, HR 0.45) in patients who had progressed on a nonsteroidal AI,[39] but there was no significant OS or quality of life (QoL) benefit.[40] None of the patients enrolled in this trial had previously received CDK4/6 inhibitors, although retrospective analyses suggest that prior exposure to CDK4/6 inhibitor therapy may not impact survival outcomes for patients receiving everolimus/exemestane.[41,42] In patients with tumours harbouring an *ESR1* mutation, substituting the exemestane backbone with fulvestrant is favoured [ESCAT score: II-A; off label].[43] If everolimus is used, appropriate prophylaxis, such as dexamethasone oral solution, should be prescribed to prevent the incidence and severity of stomatitis.[44]

In the BOLERO-6 trial comparing exemestane/everolimus with everolimus or capecitabine monotherapy,[45] everolimus/exemestane conferred a PFS benefit over everolimus alone (HR 0.74; 90% CI 0.57-0.97), thereby supporting its continued use in an endocrine-based sequence [I, B; ESMO-MCBS v1.1 score: 2]. However, this isolated PFS benefit may have been exaggerated by a high level of informative censoring.[46] For patients unlikely to tolerate exemestane/everolimus, capecitabine is a good option since the PFS and OS for these agents are not significantly different.[45]

Third-line treatment and beyond. Considerations for treatment in the third-line setting and beyond should take into account sensitivity to previous treatments received, time to progression (TTP), *gBRCAm* status, tumour biology (including other germline and somatic alterations, if results are available) and mechanisms of resistance that may have arisen during previous treatments (a tumour biopsy or ctDNA analysis could be performed, if feasible).

For patients deemed endocrine sensitive, continuation of ET with agents not previously used in the metastatic setting may represent an option to delay time to ChT and achieve some clinical benefit [III, B].

For patients considered endocrine resistant where targeted agents have already been used or ruled out due to lack of therapeutically-relevant molecular alterations, ChT should be considered [V, B].

If ChT is indicated, single agents are generally preferred over combination strategies based on QoL considerations, except for patients who need a rapid response due to disease burden, since a superior OS benefit for combination strategies has not been demonstrated and they are generally more toxic [II, A]. In *gBRCAm* carriers, PARP inhibitors are associated with an improved PFS and QoL, but not OS, compared with single-agent ChT [I, A; ESMO-MCBS v1.1 score: 4; ESCAT score: I-A].[47,48]

The optimal ChT sequence in MBC has not been established. Taxanes and anthracyclines should be considered, especially in patients who have not received these agents in an earlier setting or in patients with a DFI of ≥12 months after use of these therapies [II, B]. If available, use of liposomal anthracyclines or protein-bound paclitaxel may be considered for the rechallenge [II, B]. If rechallenge with anthracyclines is planned, attention needs to be paid to the lifetime cumulative dose limits and cardiac monitoring is mandatory.[49] Capecitabine, eribulin, vinorelbine, platinums or other agents should be discussed with patients as potential treatment options [I, A]; the reported efficacy in terms of PFS and OS, expected toxicity profile, administration route and treatment schedule all need to be explained. If capecitabine is used, patients should undergo germline variant testing for the lack of enzyme, dihydropyrimidine dehydrogenase (DPD), before treatment is initiated.[50] The combination of a taxane or capecitabine with bevacizumab, if available, is a first-line ChT option, given the reported PFS benefit versus ChT alone and lower toxicity compared with combination ChT, even in the absence of an OS benefit or improvement in QoL [I, C; ESMO-MCBS v1.1 score: 2].[51]

ChT should generally be continued until disease progression or intolerable toxicity (except for anthracyclines where the maximum cumulative dose should be taken into consideration to minimise cardiac toxicity) [II, B].[8]

Recommendations

- First-line treatment:
    - A CDK4/6 inhibitor combined with ET is the standard-of-care first-line therapy for patients with ER-positive, HER2-negative MBC, since it is

associated with substantial PFS and OS benefits and maintained or improved QoL [I, A; ESMO-MCBS v1.1 scores: 3-5].

- ET alone in the first-line setting should be reserved for the small group of patients with comorbidities or a PS that preclude the use of CDK4/6 inhibitor combinations.
- Pre- and perimenopausal women must receive OFS in addition to all endocrine-based therapies.

- Second-line treatment:
  - Selection of second-line therapy (ChT versus further ET-based therapy) should be based on disease aggressiveness, extent and organ function, and consider the associated toxicity profile.
  - Alpelisib/fulvestrant is a treatment option for patients with PIK3CA-mutant tumours (in exons 7, 9 or 20), prior exposure to an AI (± CDK4/6 inhibitors) and appropriate HbA1c levels [I, B; ESMO-MCBS v1.1 score: 2; ESCAT score: I-A].
  - Everolimus/exemestane is an option since it significantly prolongs PFS [I, B; ESMO-MCBS v1.1 score: 2]. Tamoxifen or fulvestrant can also be combined with everolimus [II, B]. If everolimus is used, stomatitis prophylaxis must be used.
  - PARP inhibitor monotherapy (olaparib or talazoparib) should be considered for patients with germline pathogenic *BRCA1/2* mutations [I, A; ESMO-MCBS v1.1 score: 4; ESCAT score: I-A] and as an option for those with somatic pathogenic or likely pathogenic *BRCA1/2* or germline *PALB2* mutations.
  - At least two lines of endocrine-based therapy are preferred before moving to ChT.
  - In patients with imminent organ failure, ChT is a preferred option.
- Beyond second line:
  - For patients with endocrine-sensitive tumours, continuation of ET with agents not previously received in the metastatic setting may represent an option [III, B].
  - Patients with tumours that are endocrine resistant should be considered for ChT [V, B].

- Sequential single-agent ChT is generally preferred over combination strategies. In patients where a rapid response is needed due to imminent organ failure, combination ChT is preferred [II, A].
- Available drugs for single-agent ChT include anthracyclines, taxanes, capecitabine, eribulin, vinorelbine, platinums and other agents.
- Rechallenge with anthracyclines or taxanes is feasible in patients with a DFI ≥12 months. If available, the use of liposomal anthracyclines or protein-bound paclitaxel may be considered for the rechallenge [II, B].
- The combination of a taxane or capecitabine with bevacizumab, if available, is an option for the first line of ChT [I, C; ESMO-MCBS v1.1 score: 2].
- If capecitabine is used, patients should undergo germline variant testing for the lack of enzyme, DPD, before starting treatment.
- ChT should generally be continued until PD or intolerable toxicity (except for anthracyclines where the cumulative limit needs to be taken into account) [II, B].
- The optimal sequence of therapy in MBC has not been established. Available options should be discussed with the patient [I, A].

HER2-positive breast cancer

First-line treatment. A proposed treatment strategy for the first- and second-line treatment of HER2-positive MBC is shown in **Figure 3**. The CLEOPATRA trial established the gold standard in the first-line setting: adding pertuzumab to docetaxel and trastuzumab increased median PFS by >6 months (18.5 vs 12.4 months with and without pertuzumab, respectively, HR 0.62; 95% CI 0.51-0.75 months; $P <$ 0.001) [I, A; ESMO-MCBS v1.1 score: 4; ESCAT score: I-A].[52] At a median follow up of >8 years, there was a 16.3-month improvement in median OS (HR 0.69; 95% CI 0.58-0.82 months) associated with the addition of pertuzumab to trastuzumab/docetaxel.[3] Docetaxel should be given for at least six cycles, if tolerated, followed by maintenance trastuzumab/pertuzumab until progression [I, A]. An alternative taxane may substitute docetaxel [II, A].

Trastuzumab/pertuzumab/taxane is recommended in the first-line setting regardless of HR status (ER and/or PgR) [I, A]. However, ET may be added to

trastuzumab/pertuzumab maintenance therapy after completing at least six cycles of upfront concomitant ChT for those with HER2-positive, HR-positive tumours [II, A].[53]

In case of patient comorbidities, personal preferences or PS preclude the use of ChT in patients with HER2-positive, HR-positive breast cancer, ET (e.g. an AI) in combination with a HER2-targeted therapy such as trastuzumab,[54,55] trastuzumab/pertuzumab,[53] trastuzumab/lapatinib,[56] or lapatinib[57] may be used [II, B]. The use of single-agent ET without a HER2-targeted therapy is not routinely recommended unless cardiac disease precludes the safe use of HER2-directed therapies [III, C]. If ChT is contraindicated in patients with HER2-positive, HR-negative tumours, HER2-targeted therapy without ChT (e.g. trastuzumab or trastuzumab/pertuzumab[58]) may be used; if taxanes are contraindicated, a less toxic ChT partner (e.g. capecitabine or vinorelbine) may be considered [III, C; off label].

It is suggested that patients with metastatic recurrence within 6-12 months of receiving adjuvant trastuzumab/pertuzumab should follow second-line therapy recommendations[4] [II, B]. However, patients who experience distant metastatic recurrence within 12 months of adjuvant trastuzumab (without pertuzumab) may receive first-line trastuzumab/pertuzumab/taxane or second-line therapy.

In view of the therapies currently used in HER2-positive EBC, general recommendations for drug rechallenge may be applied in HER2-positive MBC.

Second-line treatment. Ado-trastuzumab emtansine (T-DM1) was the gold standard second-line therapy based on consistent PFS and OS data from the EMILIA[4] and TH3RESA[59] trials which compared T-DM1 with either lapatinib/capecitabine[4] or treatment of physician's choice (TPC),[59] respectively [I, A; ESMO-MCBS v1.1 score: 4; ESCAT score: I-A]. However, data from the DESTINY-Breast-03 trial indicate that the antibody drug conjugate (ADC), fam-trastuzumab deruxtecan-nxki (trastuzumab deruxtecan), is associated with a significantly improved PFS (HR 0.28; $P = 7.8 \times 10^{-22}$) compared with T-DM1 in patients previously treated with a taxane and trastuzumab in the advanced disease setting.[60] The 12-month PFS rate was 75.8% with trastuzumab deruxtecan versus 34.1% with T-DM1. A strong trend in favour of OS benefit was also observed (HR 0.56; $P = 0.007172$), although statistical significance has not yet been reached. The objective response

rate (ORR) with trastuzumab deruxtecan was 79.7% versus 34.2% with T-DM1. Drug-related interstitial lung disease (ILD) occurred in 10.5% of patients (0.8% grade 3) but no deaths were reported. Based on the strength of these efficacy and safety data, it is reasonable to consider trastuzumab deruxtecan the new standard second-line therapy in regions where this drug is available [I, A], moving T-DM1 to a later-line setting.

Data from the randomised phase II HER2CLIMB trial support the activity of tucatinib, a HER2-selective tyrosine kinase inhibitor (TKI) with minimal inhibition of epidermal growth factor receptor (EGFR), in combination with capecitabine/trastuzumab for patients with BMs.[61] Although this trial was conducted in patients who had previously received trastuzumab and T-DM1, the PFS and OS benefits demonstrated in patients with active or stable CNS metastases (HRs 0.32 and 0.58, respectively) warrant consideration of its second-line use for selected patients with known BMs [II, A; ESMO-MCBS v1.1 score: 3; ESCAT score: I-A; FDA-approved, not European Medicines Agency (EMA)-approved].

Third-line treatment and beyond. Several drugs have been approved for use in patients with trastuzumab-, pertuzumab- and ADC-pretreated HER2-positive MBC (**Figure 4**). In the HER2CLIMB study,[62] the addition of tucatinib to trastuzumab/capecitabine increased the median PFS from 5.6 months to 7.8 months (HR 0.54; $P < 0.001$) [I, A; ESMO-MCBS v1.1 score: 3; ESCAT score: I-A; FDA-approved, not EMA-approved]. Median OS was also improved with tucatinib-based treatment (21.9 months versus 17.4 months, respectively; HR 0.66; $P = 0.005$).

Trastuzumab deruxtecan is a third-line treatment option for patients who have not received this agent in the second-line setting based on activity reported in a large, single-cohort phase II study (N = 184).[63] In heavily pretreated patients with a median of six prior lines of therapy, median PFS was 19.4 months and ORR was 61.4% (updated data).[64] However, treatment was associated with 15.2% of ILD. The case-fatality rate of 2.2% led to a ‘black box warning’ in the United States (US). [III, A; ESMO-MCBS v1.1 score: 2; ESCAT score: I-A].

T-DM1 is also a third-line treatment option for those who have not received this agent as second-line therapy [I, A; ESMO-MCBS v1.1 score: 4; ESCAT score: I-A].

Given the introduction of the new available anti-HER2 drugs, the role of lapatinib is unclear but it remains one of the possible therapy options in HER2-positive MBC. In TKI-naive patients, lapatinib/trastuzumab improves PFS (HR 0.73; *P* = 0.008) with a trend towards improved OS (HR 0.75; *P* = 0.106) compared with lapatinib alone [I, B; ESMO-MCBS v1.1 score: 4; ESCAT score: I-A].[65]

Neratinib, an irreversible pan-HER TKI, is approved by the Food and Drug Administration (FDA) in patients with pretreated HER2-positive MBC based on the NALA study, which randomised patients to receive capecitabine with either lapatinib or neratinib.[66] There was a modest improvement in PFS (HR 0.76; *P* = 0.0059) and substantial toxicity but no OS benefit [I, C; ESMO-MCBS v1.1 score: 1; ESCAT score: I-A; FDA-approved, not EMA-approved].

Margetuximab-cmkb (margetuximab), an Fc-engineered antibody derivative of trastuzumab, was evaluated in the SOPHIA trial, which randomised patients who had received ≥2 prior lines of anti-HER2 therapy to receive margetuximab plus ChT versus trastuzumab plus ChT.[67] PFS was improved with margetuximab (5.8 versus 4.9 months; HR 0.76; *P* = 0.03), but no significant OS benefit was demonstrated [I, B; ESMO-MCBS v1.1 score: 2; ESCAT score: I-A; FDA-approved, not EMA-approved]. An exploratory analysis suggested that the PFS benefit is restricted to patients with an F-allele for the *Fc-gamma receptor IIIA* gene.[67]

Continued HER2 blockade beyond disease progression is considered standard clinical practice. If the anti-HER2 therapies discussed above have been exhausted, are not considered suitable or are not available, sequential trastuzumab-based strategies (in combination with different ChTs) should be considered [III, A].

Recommendations

- First line treatment:

- Standard first-line treatment of HER2-positive MBC should be pertuzumab/trastuzumab/docetaxel regardless of HR status [I, A; ESMO-MCBS v1.1 score: 4; ESCAT score: I-A].
- Docetaxel should be given for at least six cycles if tolerated, followed by maintenance pertuzumab/trastuzumab until progression [I, A].
- An alternative taxane (paclitaxel, nab-paclitaxel) may be substituted for docetaxel [II, A].
- ET may be added to pertuzumab/trastuzumab maintenance after completion of ChT for HER2-positive, HR-positive tumours. OFS should also be added for pre- and perimenopausal women.
- If ChT is contraindicated in patients with HER2-positive, HR-negative BC, HER2-targeted therapy without ChT (e.g. trastuzumab or trastuzumab/pertuzumab) may be used; if taxane ChT is contraindicated, a less toxic ChT partner (e.g. capecitabine or vinorelbine) may be considered [III, C].
- In selected cases of HER2-positive, HR-positive breast cancer where the patient is not suitable for first-line ChT, ET (e.g. an AI) in combination with a HER2-targeted therapy such as trastuzumab,[54,55] trastuzumab/pertuzumab,[53] trastuzumab/lapatinib[56] or lapatinib[57] may be recommended [II, B].
- The use of single-agent ET without HER2-targeted therapy in HER2-positive, HR-positive MBC is not routinely recommended unless comorbidities (e.g. cardiac disease) preclude the safe use of HER2-directed therapies [III, C].
- It is suggested that patients with metastatic recurrence within 12 months of receiving adjuvant trastuzumab/pertuzumab should follow second-line therapy recommendations [II, B].

- Second-line treatment:
  - Trastuzumab deruxtecan should be given as second-line therapy after progression on a taxane and trastuzumab [I, A].

  - T-DM1 is a second-line treatment option after progression on a taxane and trastuzumab in cases where trastuzumab deruxtecan is not available [I, A; ESMO-MCBS v1.1 score: 4; ESCAT score: I-A].
  - Tucatinib/capecitabine/trastuzumab or trastuzumab deruxtecan may be used in the second-line setting in selected patients with BMs [II, A].

- Treatment options for third line and beyond:
  - Tucatinib/capecitabine/trastuzumab [I, A; ESMO-MCBS v1.1 score: 3; ESCAT score: I-A; FDA-approved, not EMA-approved], trastuzumab deruxtecan [III, A; ESMO-MCBS v1.1 score: 2; ESCAT score: I-A; FDA-approved, not EMA-approved] and T-DM1 [I, A; ESMO-MCBS v1.1 score: 4; ESCAT score: I-A] appear to be the most active treatment options in the third-line setting. The choice of treatment depends on prior second-line therapy, patient characteristics, toxicity profile and availability.
  - In later lines of therapy, lapatinib is an evidence-based therapy option to be used preferably in combinations (e.g. with capecitabine, trastuzumab or ET) [I, C].
  - Neratinib [I, C; ESMO-MCBS v1.1 score: 1; ESCAT score: I-A; FDA-approved, not EMA-approved], and margetuximab [I, B; ESMO-MCBS v1.1 score: 2; ESCAT score: I-A; FDA-approved, not EMA-approved] can be considered reasonable approaches in the late-line scenario. Although there are no comparative data, the most appropriate setting might be in patients who have exhausted all standard therapy options [V, C]. However, in HER2-positive MBC there is no evidence for sequencing a TKI after a TKI.

- Continued anti-HER2-based therapy is the current clinical standard for patients with HER2-positive tumours. If other anti-HER2 therapies have been exhausted, are not considered suitable or are not available, trastuzumab beyond progression should be considered [III, A].

TNBC

Definitions. Initially 'triple negative' BCs were defined by the absence of expression of ER and PgR receptors and of overexpression of HER2 or amplification of *HER2neu*. This implies that this category of BCs is not defined by a theragnostic characteristic (see pathology section). According to this definition, they represent ~15%-20% of all BCs.[68] Further details of TNBC definitions can be found in the **supplementary text – section 2**, available at *Annals of Oncology* online.

First-line systemic treatment strategies. A proposed treatment strategy for the management of metastatic triple negative breast cancer (mTNBC) is shown in **Figure 5.** For most TNBCs, ChT remains the standard treatment. However, specific data concerning mTNBCs treated by historical but still relevant ChTs are missing. In the first line, establishment of PD-L1 and *gBRCAm* status is paramount since they enable management optimisation.

PD-L1-positive mTNBC. Three trials have addressed the question of adding an immune checkpoint inhibitor (ICI) to ChT in mTNBC,[69-71] two with atezolizumab[70,71] and one with pembrolizumab[69] (**supplementary Table S3**, available at *Annals of Oncology* online).

For atezolizumab, two trials have addressed the same question: IMpassion130 evaluated atezolizumab plus nab-paclitaxel[70] whereas IMpassion131 evaluated atezolizumab plus paclitaxel.[71] IMpassion130 had co-primary endpoints of PFS and OS in the intention-to-treat (ITT) population and had a hierarchal design that allowed for formal evaluation of OS in the PD-L1-positive population only if the OS in the ITT population was significantly improved by the addition of atezolizumab. In the ITT population, atezolizumab provided a PFS benefit of 7.2 versus 5.5 months with a HR of 0.8 (95% CI 0.69-0.92; $P = 0.002$). In the PD-L1-positive group, atezolizumab provided a PFS benefit of 7.5 versus 5 months with a HR of 0.62 (95% CI 0.49-0.78; $P < 0.001$). In the ITT population, there was no significant benefit in OS with the addition of atezolizumab; median OS was 21.3 months versus 17.6 months (HR 0.84; 95% CI 0.69-1.02; $P = 0.08$). However, despite the hierarchical statistical design, an analysis in the PD-L1-positive population was conducted, which showed an OS of 25 months versus 15.1 months favouring the atezolizumab arm (an

updated efficacy analysis reported a smaller OS difference of 25 versus 18 months[70]). Based on these data, atezolizumab/nab-paclitaxel was approved by the EMA (but has been withdrawn from the FDA approval process by the manufacturer due to lack of confirmatory data) and may be considered an option in the first-line setting in patients with *de novo* MBC or a DFI ≥12 months whose tumours have PD-L1 expression ≥1% based on staining of the immune cells [II, A; ESMO-MCBS v1.1 score: 3; ESCAT score: I-A; EMA-approved, not FDA-approved].

Unlike the IMpassion130 results, in the PD-L1-positive population of IMpassion131, atezolizumab did not significantly improve PFS or OS compared with placebo. It is unclear if steroid use with solvent-based paclitaxel played any role in dampening the effect of the immune response (although benefit was seen in KEYNOTE-355 where steroids were used in two of the three ChT arms[69]) or if other potential reasons, such as patient heterogeneity, paclitaxel backbone (given the fact that paclitaxel is usually already given in the EBC setting) or the unusually good outcome of the control group, played a role in the differing results between these two trials.

In KEYNOTE-355, enrolled patients were similar to the IMpassion130 population, except that a 6-month DFI following adjuvant therapy was permitted as opposed to 12 months. In this study, the primary endpoint was considered only in PD-L1-positive patients, defined as combined positive score (CPS) ≥10. The primary endpoint was met with PFS significantly improved with the addition of pembrolizumab to ChT (nab-paclitaxel, paclitaxel or gemcitabine/carboplatin) (9.7 versus 5.6 months; HR 0.65; CI 0.49-0.86; *P* = 0.0012) in patients with PD-L1-positive (CPS ≥10) tumours.[69] In the final analysis, pembrolizumab plus ChT was also associated with a significant OS benefit (23.0 versus 16.1 months; HR 0.73; 95% CI 0.55-0.95; *P* = 0.0093) and a greater ORR (52.7% versus 40.8%), disease control rate (65.0% versus 54.4%) and duration of response (DoR; 12.8 versus 7.3 months) in patients with PD-L1-positive (CPS ≥10) tumours. The PFS benefit of pembrolizumab was consistent with prior results.[72] Based on these data, it is reasonable to consider pembrolizumab/ChT in patients with *de novo* advanced/metastatic disease or disease that has progressed at least 6 months after completion of (neo)adjuvant ChT in tumours with PD-L1 expression CPS ≥10 [I, A; ESMO-MCBS v1.1 score: 3; ESCAT score: I-A; FDA-approved, not EMA-approved].

Interestingly, both KEYNOTE-355 and IMpassion130 had similar HRs for OS effect in their PD-L1-positive populations, despite the different PD-L1 assay, ChT backbone and ICI agent. However, these three studies also highlight the difficulties regarding PD-L1 assays (which are linked to different pharmaceutical companies), which one to use, and the role of ICIs in combination with ChT in the case of a short DFI (i.e. <6 months).

gBRCAm mTNBC. Carboplatin may be considered as a superior treatment option to docetaxel, since median PFS was improved but only by 2.6 months without an OS benefit.[73] PARP inhibitors are recommended [I, A; ESMO-MCBS v1.1 score: 4; ESCAT score: I-A] (see section on hereditary breast cancer).

PD-L1-negative and gBRCA-wild type mTNBC. The initial treatment is ChT. Several options are possible according to previous treatment exposure in the EBC setting, DFI and disease presentation. If the patient has no prior exposure to anthracyclines and no medical contraindications, the options are anthracyclines or taxanes as monotherapy,[74] or various combinations incorporating these two drugs together or not. Nab-paclitaxel/carboplatin is also a valid option since it demonstrated superiority in PFS compared with nab-paclitaxel/gemcitabine or carboplatin/gemcitabine.[75]

Regarding the question of single-agent versus combination ChT, although a Cochrane review found that combination ChT was associated with a longer OS when compared with single-agent therapy (HR 0.88; 95% CI 0.83-0.94; $P < .001$), the clinical benefit was modest and at the cost of increased toxicity.[76] Few of these trials systematically investigated the combination versus sequential approach, assessed differences in QoL or focused on mTNBC. For these reasons, and the fact that a higher ORR was achieved with combination regimens (odds ratio 1.28; 95% CI 1.15-1.42; $P < .001$), this approach is not considered a standard but could be preferred in cases of imminent organ failure.

There is a paucity of trials addressing the question of bevacizumab plus ChT combinations in mTNBC. However, a pooled analysis of several phase III trials showed that in patients with mTNBC, the addition of bevacizumab to paclitaxel or

capecitabine improved PFS (HR 0.63; 95% CI 0.52-0.76) with a 2.7-months absolute improvement in PFS but no improvement in OS.[51] Therefore, bevacizumab plus either paclitaxel or capecitabine are also therapeutic options in the first-line setting in countries where bevacizumab is available [ESMO-MCBS v1.1 score: 2].

Progression after anthracyclines and taxanes. The ADC, sacituzumab govitecan-hziy (sacituzumab; FDA-approved, not EMA-approved), received accelerated FDA approval in mTNBC based on a single arm, phase I/II dose escalation, dose expansion study (IMMU-132-01).[77] In this trial, the mTNBC cohort comprised 108 patients who had received ≥2 prior therapies for metastatic disease who were treated at the recommended phase II dose of 10 mg/kg on days 1 and 8 of a 21-day cycle (q3w). The ORR was 33% (95% CI 24.6-43.1), with 2.8% complete responses (CRs) and 30.6% partial responses (PRs), and a median DoR of 7.7 months (95% CI 4.9-10.8). Adverse reactions occurring in ≥25% of patients included nausea, neutropaenia, GI complications, rash and alopecia. Notably, patients homozygous for the *UGT1A1*28* genotype had an increased risk of severe neutropaenia and diarrhoea, resulting in a 'black box warning'. The confirmatory phase III ASCENT trial included 529 patients with TNBC who had received a range of 2-17 prior treatments for MBC.[5] PFS was improved from 1.7 to 5.6 months (HR 0.41; 95% CI 0.32-0.52; $P < 0.001$) and OS from 6.7 to 12.1 months (HR 0.48; 0.38-0.59; $P < 0.0001$) compared with eribulin, vinorelbine, capecitabine or gemcitabine. ORR was also increased from 5% to 35%. Selection for Trop2 expression did not significantly affect efficacy.[78] Based on these results, sacituzumab has received FDA approval but is not currently EMA-approved. It might be considered as the preferred treatment option after anthracyclines and taxanes, particularly if patients have also received carboplatin and capecitabine in the adjuvant setting and if no theragnostic markers are available such as *gBRCAm* [ESMO-MCBS v1.1 score: 4; FDA-approved, not EMA-approved]. After progression on sacituzumab, all ChT recommendations for HER2-negative disease also apply for TNBC such as eribulin, capecitabine and vinorelbine.

ICI monotherapy in later lines for advanced TNBC is not recommended due to low response rates, as seen in the KEYNOTE-119 trial. However, although pembrolizumab monotherapy does not improve OS versus ChT, there does not

appear to be any deleterious effect on this endpoint using ICI monotherapy versus ChT in the ITT population. In addition, the benefit of pembrolizumab compared with single-agent ChT increased depending on CPS, with a significant OS benefit versus ChT seen in cases of CPS ≥20.[79] Therefore, it seems reasonable to discuss the option of pembrolizumab treatment for patients with tumours strongly positive for PD-L1 if they have not been exposed to ICI therapy in a previous line or do not have access to a clinical trial.

Maintenance. No phase III study has specifically addressed the question of maintenance therapy in TNBC. Although a longer duration of ChT is associated with a better outcome in MBC, it also increases the risk of toxicity.[8] However, for patients who have received an initial ChT/ICI combination, ICI maintenance is acceptable in the absence of safety issues. The place of ICI as a maintenance treatment after induction ChT alone is still an area of debate, although some preliminary data are encouraging (see **supplementary Table S3**, available at *Annals of Oncology* online).[80] Similarly, bevacizumab maintenance may be used after an initial bevacizumab/taxane or bevacizumab/capecitabine combination.

Recommendations

- First-line treatment:
    - If PD-L1-positive, the preferred option is ChT in combination with an ICI.
        - In case of PD-L1 immune cell positivity (Ventana SP142), atezolizumab plus nab-paclitaxel where the DFI is ≥12 months in countries where this indication is approved [II, A; ESMO-MCBS v1.1 score: 3; ESCAT score: I-A; EMA-approved, not FDA-approved].
        - In case of CPS ≥10, pembrolizumab plus paclitaxel, nab-paclitaxel or carboplatin/gemcitabine where the DFI is ≥6 months [I, A; ESMO-MCBS v1.1 score: 3; ESCAT score: I-A; FDA-approved, not EMA-approved].
    - If *gBRCAm* and PD-L1-negative, the preferred options are olaparib or talazoparib [I, A; ESMO-MCBS v1.1 score: 4; ESCAT score: I-A] or ChT

with carboplatin [II, A] (see below).

- If PD-L1-negative and *gBRCA* wild type, the preferred option depends on previous treatment exposure, disease presentation, DFI and patient considerations.
  - Taxane monotherapy is the most frequent option.
  - Anthracyclines are an option in cases of no prior exposure or if rechallenge is possible.
  - In case of imminent organ failure, combination therapy is preferred based on a taxane and/or anthracycline combination and including bevacizumab (first line only) if available.

- Progression after anthracyclines and taxanes:
  - Sacituzumab (if available) is the preferred treatment option after taxanes [I, A; ESMO-MCBS v1.1 score: 4; FDA-approved, not EMA-approved].
  - After progression, all ChT recommendations for HER2-negative disease also apply for TNBC such as eribulin, capecitabine and vinorelbine.
  - There is no data to support antiandrogen therapy, or inhibitors targeting PI3K, HER2 or AKT for advanced TNBC and therefore these cannot be recommended for routine clinical use outside a clinical trial.

Hereditary BC (gBRCAm)

Two randomised studies of patients with HER2-negative, *gBRCAm* MBC previously treated with anthracyclines and/or taxanes demonstrated that treatment with a PARP inhibitor (olaparib, talazoparib) resulted in statistically significant improvements in PFS compared with capecitabine, vinorelbine, eribulin or (in one study) gemcitabine.[47,48] OS was not improved but a *post hoc* subset analysis of one study suggested improved OS in patients receiving olaparib who had not received prior ChT for metastatic disease.[81] Notably, over 40% of the control arm in each study received a platinum or PARP inhibitor after progression on study treatment.

The patients enrolled in the pivotal trials were largely women. However, there is no plausible biological reason to expect lower efficacy in men with MBC and *gBRCAm*. Eligibility criteria for the studies included prior treatment with (or

inappropriateness for) anthracycline/taxane ChT. This selection was guided by regulatory considerations rather than a biological rationale. Therefore, PARP inhibitors should not be withheld from patients without prior anthracycline/taxane treatment. Indeed, based on the subset analysis of OlympiAD, requiring progression on these agents in the metastatic setting may be associated with a lower magnitude of OS benefit. Patients with HR-positive MBC and *gBRCAm* do benefit from PARP inhibitor treatment, with no statistical evidence of heterogeneity of effect in either of the pivotal phase III trials.

Platinum-based ChT (single agent or combined with paclitaxel) is associated with a substantial PFS benefit in patients with MBC and *gBRCAm*.[73,82] Median PFS with paclitaxel and carboplatin in the BROCADE-3 study was 12.6 months but there was no single-agent ChT arm for comparison.[82] In TNBC, PFS with first-line single-agent carboplatin was superior to single-agent docetaxel only in patients with *gBRCAm*.[73] There are no studies directly comparing PARP inhibitors with a platinum agent (either alone or in combination with other ChT agents or ICIs). It should be noted that in the pivotal trials, health-related quality of life (HRQoL) was better with PARP inhibitors compared with ChT.[83,84] There are no studies comparing PARP inhibitors with ET (alone or with targeted therapies) in patients with HR-positive disease. Decisions about sequencing of PARP inhibitors with other treatments should be based on factors such as prior treatment response, disease burden, PD-L1 status, *PIK3CA* status, HR status and the relative toxicities of the different approaches.

Further details regarding the management of hereditary BC can be found in the **supplementary text – section 3**, available at *Annals of Oncology* online.

Recommendations

- Patients with HER2-negative MBC and germline pathogenic or likely pathogenic variants in *BRCA1* or *BRCA2* should be offered treatment with a PARP inhibitor (olaparib or talazoparib) independent of HR status as an alternative to ChT [I, A; ESMO-MCBS v1.1 score: 4; ESCAT score: I-A].
- Prior treatment with anthracyclines/taxanes should not be required before offering patients with MBC and *gBRCAm* treatment with a PARP inhibitor; nor should HR-positive patients be required to demonstrate complete endocrine resistance [I, D].

- There is insufficient evidence to determine the optimal sequencing of PARP inhibitors with other active treatments such as ChT/ICI combinations in mTNBC or ET and targeted therapy combinations in HR-positive disease [I, A].
- Patients who may be considered for treatment with a PARP inhibitor should be offered genetic testing for pathogenic variants in *BRCA1* and *BRCA2* regardless of age, family history or breast cancer subtype [I, A].

Site-specific management

Details regarding the management of primary stage IV BC, oligometastatic disease (OMD), bone metastases, BMs and leptomeningeal metastases (LMs) can be found in the **supplementary text – section 4**, available at *Annals of Oncology* online. A proposed treatment algorithm for the management of OMD is shown in **Figure 6**.

Recommendations

- Primary stage IV disease
    - For patients with newly diagnosed stage IV BC and an intact primary tumour, therapeutic decisions should ideally be discussed in a multidisciplinary context [II, B].
    - LRT of the primary tumour in the absence of symptomatic local disease does not lead to an OS benefit and is thus not routinely recommended [II, D].
    - In patients with local symptoms caused by the primary tumour or metastatic disease, the use of local treatment modalities should be evaluated [II, A].
    - Surgery of the primary tumour may be considered for patients with bone-only metastasis, HR-positive tumours, HER2-negative tumours, patients <55 years, patients with OMD and those with a good response to initial systemic therapy [II, B].
- OMD
    - The dynamics in chronic metastatic conditions should be reviewed to identify induced/recurrent OMD.[85] Complete imaging history should be available for decisions on OMD care [V, C].

- Patients with OMD should be discussed in a multidisciplinary context to individualise management [V, C].
- Multimodality treatment approaches involving LRT [e.g. high conformal radiotherapy (RT), image guided ablation, selective internal radiotherapy (SIRT) and/or surgery] combined with systemic treatments are recommended, tailored to the disease presentation in the individual patient [V, C].
- Local ablative therapy to all metastatic lesions may be offered on an individual basis after discussion in a multidisciplinary setting [II, C]; however, it is unknown if this leads to improved OS.

- Bone metastases and bone modifying agents (BMAs)
  - A multidisciplinary approach is essential to manage patients with bone metastases and prevent skeletal-related events (SREs) [V, A].
  - An orthopaedic evaluation is advised in case of significant lesions in long bones or vertebrae as well as in patients with metastatic spinal cord compression (MSCC) to discuss the possible role of surgery [IV, A].
  - RT is recommended for lesions at moderate risk of fracture and those associated with moderate to severe pain [I, A].
  - A single 8 Gy RT fraction is as effective as fractionated schemes in uncomplicated bone metastases [I, A].
  - RT should be delivered after surgery for stabilisation or separation surgery for MSCC [III, B].
  - BMAs, e.g. bisphosphonates or denosumab, are recommended for patients with bone metastases, regardless of symptoms [I, A].
  - Zoledronate can be administered every 12 weeks in patients with stable disease after 3-6 monthly treatments [I, B].
  - Denosumab should be administered every 4 weeks and is more effective than zoledronate in delaying first and subsequent SREs [I, B].
  - Before BMA initiation, patients should have a complete dental evaluation and ideally complete any required dental treatment. Calcium and vitamin D supplements should be prescribed [III, A].

- The optimal duration of BMA therapy has not been defined but it is reasonable to interrupt therapy after 2 years for patients in remission [II, B].[86]
- The ideal sequence of therapies has not been defined but it seems reasonable to document tumour response with a systemic treatment before suggesting LRT [V, C].

- BMs and LMs
  - BMs should be managed according to the recommendations outlined in the EANO-ESMO Clinical Practice Guideline (CPG) for the management of patients with BMs from solid tumours.[87]
  - LMs should be treated according to the recommendations outlined in the EANO-ESMO CPG for the management of patients with LMs from solid tumours.[88]

New drugs

Recent advances and emerging therapies for MBC are described in the **supplementary text – section 5**, available at *Annals of Oncology* online.

PERSONALISED MEDICINE

In MBC, standard therapies are personalised based on biomarkers, as described in the respective sections. In addition, there are now several tissue and site-agnostic approvals. For example, both larotrectinib [ESMO-MCBS v1.1 score: 3; ESCAT score: I-C] and entrectinib [ESMO-MCBS v1.1 score: 3; ESCAT score: I-C] are approved for patients with solid tumours expressing a *neurotrophic tyrosine receptor kinase (NTRK)* gene fusion, and pembrolizumab is approved for patients with unresectable or metastatic microsatellite instability-high/mismatch repair deficient solid tumours who have progressed and have no alternative treatment options [ESCAT score: I-C]. As such, these biomarkers need to be checked once subtype-specific standard therapies have been exhausted. For personalised therapy approaches, ESCAT classifications[89] need to be considered (**supplementary Table S1**, available at *Annals of Oncology* online). Currently, new drugs (e.g. ADCs) are being evaluated in MBC that have documented activity across several subtypes and

may require assessment of new biomarkers (e.g. HER2-low, HER3) once therapeutic efficacy and biomarker validation have been completed.

LONG-TERM IMPLICATIONS AND SURVIVORSHIP

In MBC, regular assessments of disease status and therapy toxicities should include clinical assessments, blood tests, imaging and patient-reported outcomes (PROs). Principles of disease monitoring by imaging are discussed under Staging.

Side effects

General principles. Decisions regarding the systemic treatment of MBC should be based on a balanced consideration of the predicted response to a particular treatment strategy and associated tolerability and AEs. Management of side effects should be according to the respective ESMO CPGs.[90] Particular attention must be paid to the incidence and risk of side effects in specific populations, such as elderly patients and those with comorbidities, in order to ensure therapy adherence. Proactive symptom management and education helps to alleviate side effects and improves QoL [I, A].

PRO measures capture the patient experience and perceived impact of treatment and toxicity on health status. PROs include areas of HRQoL as well as patient satisfaction with care.[91]

Further details regarding the management of common and therapy-specific toxicities can be found in the **supplementary text – section 6**, available at *Annals of Oncology* online.

Recommendations

- An interdisciplinary approach is critical, including specialised oncology and/or breast care nurses to proactively screen for and manage treatment-emergent toxicities.
- Patients should be informed about treatment choices and side effect profiles of recommended systemic treatments.

- All treatment should include formal patient education regarding side effect management [I, A].
- Careful assessment of side effects should occur at each visit. ePROs may be useful in this context.
- QoL assessments should be incorporated into the evaluation of treatment efficacy.
- Dose reduction and delay are effective strategies to manage toxicity in advanced disease [I, A].

Palliative care

Palliative care is an area of high importance in oncology and ESMO has published several CPGs in this field which also apply to the management of patients with MBC.[90] Palliative care should be integrated early and offered both in an inpatient and an outpatient setting.

General principles of care. For patients with MBC, median OS is increasing with the introduction of new treatments and patients are more likely to experience metastases in many areas of the body.[92] As well as receiving the best available treatment, patients should be offered optimal symptom control, psychological, social and spiritual support. Many areas of care need to be managed, including pain, dyspnoea, cachexia, fatigue, depression and anxiety, which should also consider comorbidities, previous treatments, age and patient preferences. Shared decision-making between the patient and health care professionals, as well as good communication and relationship building with the patient, family members and caregivers, is therefore paramount to ensure a mutual understanding of treatment expectations and goals.

The emotional toll of caring for patients who are dying also has an impact on healthcare staff, and processes should be in place to support their mental health, enabling them to continue to provide sensitive and effective care.

Patient perspective

Insights into the patient perspective of an MBC diagnosis and treatment can be found in the **supplementary text – section 7**, available at *Annals of Oncology* online.

METHODOLOGY

This CPG was developed in accordance with the ESMO standard operating procedures for CPGs development (http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology). The relevant literature has been selected by the expert authors. An ESMO-MCBS table with ESMO-MCBS scores is included in **Supplementary Table S4**, available at *Annals of Oncology* online. ESMO-MCBS v1.1[93] was used to calculate scores for new therapies/indications approved by the EMA and/or the FDA (https://www.esmo.org/Guidelines/ESMO-MCBS). The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee. The FDA/EMA approval status of new therapies/indications are correct at the time of writing this CPG. ESCAT scores have been defined by the authors and validated by the ESMO Translational Research and Precision Medicine Working Group.[89] Levels of evidence and grades of recommendation have been applied using the system shown in **Supplementary Table S5**, available at *Annals of Oncology* online.[94] Statements without grading were considered justified standard clinical practice by the authors.

ACKNOWLEDGEMENTS

Mark Robson is supported by an IH/NCI Cancer Center Support Grant P30 CQA008748 and the Breast Cancer Research Foundation. Sherene Loi is supported by the National Breast Cancer Foundation of Australia Endowed Chair and the Breast Cancer Research Foundation, New York. Manuscript editing support was provided by Jennifer Lamarre (ESMO Guidelines staff) and Angela Corstorphine of Kstorfin Medical Communications Ltd (KMC); this support was funded by ESMO. Nathan Cherny, Chair of the ESMO-MCBS Working Group, Urani Dafni ESMO-MCBS Working Group Member/Frontier Science Foundation Hellas and Giota Zygoura of Frontier Science Foundation Hellas provided review and validation of the

ESMO-MCBS scores. Nicola Latino (ESMO Scientific Affairs staff) provided coordination and support of the ESMO-MCBS scores and Angela Corstorphine and Sian-Marie Lucas of KMC provided medical writing and editing support in the preparation of the ESMO-MCBS table; this support was funded by ESMO. Joaquin Mateo (ESMO Translational Research and Precision Medicine Working Group) provided validation support for ESCAT scores.

FUNDING

No external funding has been received for the preparation of these guidelines. Production costs have been covered by ESMO from central funds.

DISCLOSURE

FA reports receipt of research funding and has served as speaker/advisor (compensated to the hospital) for Roche, AstraZeneca, Daiichi Sankyo, Pfizer, Novartis, Lilly.

CHB reports grants/research support (to the institution) from Pfizer, Novartis, Amgen, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Roche/Genentech, Lilly, Sanofi, Taiho Pharmaceutical, Mylan, Merrimack, Merck, AbbVie, Astellas Pharma, BioMarin, Bristol-Myers Squibb, Daiichi Sankyo, Abraxis Biosciences, AB Science, Asana Biosciences, Medivation, Exelixis, ImClone Systems, LEO Pharma, Millennium, Merck KGaA, Shanghai Henlius Biotech, Polyphor, PharmaMar; ownership or stocks in Biomarker, Tummi, MEDSir; advisory boards and consulting for Boehringer-Ingelheim, GSK, Novartis, Pfizer, Roche/Genentech, Eisai, Bayer, MSD, Astra Zeneca, Zodiac, Lilly, Sanofi.

JC has served as a consultant/advisor for Roche, Celgene, Cellestia, AstraZeneca, Seattle Genetics, Daiichi Sankyo, Erytech, Athenex, Polyphor, Lilly, Merck Sharp & Dohme, GSK, Leuko, Bioasis, Clovis Oncology, Boehringer Ingelheim, Ellipses, Hibercell, BioInvent, Gemoab, Gilead; received honoraria from Roche, Novartis, Celgene, Eisai, Pfizer, Samsung Bioepis, Lilly, Merck Sharp & Dohme, Daiichi Sankyo; received research funding to the Institution from Roche, Ariad Pharmaceuticals, AstraZeneca, Baxalta GMBH/Servier Affaires, Bayer Healthcare,

Eisai, F.Hoffman-La Roche, Guardanth Health, Merck Sharp & Dohme, Pfizer, Piqur Therapeutics, Puma C, Queen Mary University of London; owns stock, patents and intellectual property for MedSIR; received travel, accommodation, expenses from Roche, Novartis, Eisai, Pfizer, Daiichi Sankyo.

GC has served as consultant or advisor for Roche, Lilly, Bristol-Myers Squibb; served on a speaker's bureau for Roche, Pfizer, Lilly; received travel funding from Pfizer, Roche; received honoraria from Roche, Pfizer, Lilly, Novartis, AstraZeneca, SeaGen, all outside the submitted work.

EdA reports honoraria and/or advisory boards for Roche/Genentech, Novartis, Seattle Genetics, Zodiacs, Libbs and Pierre Fabre, Lilly; travel grants from Roche/ Genentech, GSK/Novartis; research grants for his institute from Roche/ Genentech, Astra-Zeneca, Novartis, Servier.

AD reports research funding to institute from Genentech, Novartis, Pfizer, Calithera.

RD reports research funding from AstraZeneca; honoraria for consultancy/advisory board participation from AstraZeneca, Eisai, Lilly, Novartis, Pfizer, Roche.

DF reports honoraria for participation in symposia from Roche.

AG reports honoraria for advisory boards from AstraZeneca, Daiichi-Sankyo, Eisai, Lilly, Novartis, Pfizer, Roche; honoraria for lectures from Eisai, Lilly; honoraria for expert testimony from Gentili.

JG has served as a consultant/advisor for Astra Zeneca, Daiichi Sankyo, Eisai, Exact Science, Lilly, Merck, Novartis, Pfizer, Pierre Fabre, Roche-Genentech, Seattle Genetics; received honoraria from AGM communication, Amgen, AstraZeneca, Daiichi-Sankyo, Decision Santé, Edimark, Eisai, Exact Science, Kephren, Lilly, Merck, Novartis, Pfizer, Pierre Fabre, Roche/Genentech, Seattle Genetics; received research funding to the Institution from Eisai, Exact Science, Roche/Genentech; is an ABC Global Alliance member; has a leadership role in AROMe and Nice St Paul de Vence Cours; is involved in educational programmes for ESO.

NH reports honoraria for lectures, advisory boards and/or personal fees from Amgen, AstraZeneca, Daiichi-Sankyo, Lilly, MSD, Novartis, Pfizer, Pierre Fabre, Roche,

Sandoz, Seagen; minority ownership interest in the West German Study Group (WSG).

SAH reports contracted research paid to institution from Ambrx, Amgen, Astra Zeneca, Arvinas, Bayer, Cytomx, Daiichi-Sankyo, Dignitana, Genentech/Roche, Gilead, GSK, Immunomedics, Eli Lilly, Macrogenics, Novartis, Pfizer, OBI Pharma, Pieris, PUMA, Radius, Sanofi, Seattle Genetics/Seagen, Zymeworks, Phoenix Molecular Designs, Ltd., Samumed; Unpaid Steering committee member for Novartis, Lilly, Daiichi-Sankyo/AZ, Genentech/Roche, Sanofi; travel expenses from Lilly (2019); uncompensated consulting/advisory boards for 4DPharma, Ambrx, Amgen, Artios, Arvinas, Daiichi Sankyo, Dantari, Genentech/Roche, Immunomedics, Macrogenics, Eli Lilly, Novartis, NK Max, Pieris, Pyxis, Seagen, Biotheranostics, Loxo.

SAI reports advisory board participation (uncompensated) for Amgen, AstraZeneca, Daiichi-Sankyo, Eisai, GSK, Hanmi, Lilly, MSD, Novartis, Pfizer, Roche; receipt of research funding/clinical trial budget from AstraZeneca, Dae Woong, Daiichi-Sankyo, Eisai, Hanmi, Pfizer, Roche.

DK reports honoraria from the European School of Oncology, MSD; non-renumerated membership of American Society for Clinical Oncology, American Society for Radiation Oncology, Arbeitsgemeinschaft Gynäkologische Onkologie, Arbeitsgemeinschaft Radiologische Onkologie, Deutsche Gesellschaft für Radioonkologie, Deutsche Gesellschaft für Senologie, European Society for Radiotherapy and Oncology, The Radiosurgery Society.

WGK reports institutional research funding by the German Research Foundation and the medical faculty of LMU Munich; serves as a non-compensated committee member of the European Organisation for Research and Treatment of Cancer and the European Society of Oncologic Imaging.

SLoi reports research funding to her institution from Novartis, Bristol Meyers Squibb, Merck, Puma Biotechnology, Eli Lilly, Nektar Therapeutics, Astra Zeneca, Roche-Genentech, Seattle Genetics; consultancy (not compensated) to Seattle Genetics, Novartis, Bristol Meyers Squibb, Merck, AstraZeneca, Roche-Genentech; consultancy (paid to institution) to Aduro Biotech, Novartis, GlaxoSmithKline, Roche-Genentech, Astra Zeneca, Silverback Therapeutics, G1 Therapeutics, PUMA

Biotechnologies, Pfizer, Gilead Therapeutics, Seattle Genetics, Bristol Meyers Squibb; Scientific Advisory Board Member of Akamara Therapeutics.

SLoibl reports honoraria for advisory boards (to institute) from Bayer, BMS, Eirgenix, GSK, Lilly, Merck; honoraria for lecture (to institute) from Samsung; honoraria for advisory boards and lectures (to institute) from Pierre Fabre, Prime/Medscape; grants and honoraria for advisory boards (to institute) from Abbvie, Celgene; grants and honoraria for advisory boards and lectures (to institute) from AstraZeneca; grants, non-financial support and honoraria for advisory boards, lectures and medical writing (to institute) from Daiichi-Sankyo, Novartis, Pfizer, Roche; grants, non-financial support and honoraria for advisory boards and medical writing (to institute) from Immunomedics/Gilead, non-financial support and honoraria for advisory boards and medical writing (to institute) from Puma, SeaGen; non-financial support and honoraria for advisory boards (to institute) from Amgen; all outside the submitted work. In addition, SLoibl has patents EP14153692.0, EP21152186.9, EP19808852.8 and Digital Ki67 Evaluator pending and patent EP15702464.7 issued, with royalties paid.

SPS reports honoraria and/or advisory board and/or speaker's bureau and/or travel funding from Roche, Pfizer, Eli Lilly, Novartis, Astra Zeneca, MSD, Exact Sciences, Nanostring. Institutional research funding from SPCC, Pfizer.

FPL has received honoraria and/or advisory board and/or speaker's bureau and/or travel funding from Roche, Pfizer, Eli Lilly, Novartis, Astra Zeneca, MSD, SeaGen, Illumina, Exact Sciences, Myriad, Nanostring; institutional research funding from Astrazeneca, Roche, MSD, Illumina.

JR reports honoraria or research grants (to the institution) from Terumo, Sirtex Medical, Boston Scientifc, Roche, Astra Zeneca.

MR reports honoraria from Research to Practice, Intellisphere, Physicians' Education Resource; consultant or advisor for Artios Pharma (uncompensared), AstraZeneca (uncompensated), Change Healthcare, Daiichi-Sankyo (uncompensated), Epic Sciences (uncompensated), Merck (uncompensated), Pfizer (uncompensated), Zenith Pharmaceuticals (uncompensated); research funding to institute from AstraZeneca, Merck, Pfizer; editorial services for AstraZeneca, Pfizer.

HSR reports research support for clinical trials through the University of California from Pfizer, Merck, Novartis, Lilly, Roche, Daiichi, Seattle Genetics, Macrogenics, Sermonix, Boehringer Ingelheim, Polyphor, AstraZeneca, Ayala, Gilead; Honoraria from Puma (grant reviews for the US National Comprehensive Cancer Network 2021, steering committee 2020), Mylan (educational talk 2019), Samsung (educational talk and consultant 2019) and Napo Pharmaceuticals, Inc (consultant). **CFS** reports institutional research funding from Amgen, AstraZeneca, Daiichi-Sanyko, the US Dept of Defence; travel funding and speaker honoraria from Novartis, AstraZeneca, Roche, Amgen.

PS reports honoraria for participation in advisory boards and satellite symposia from AstraZeneca, Bayer, Boehringer Ingelheim, Merck, Novartis, Pfizer, Puma, Roche, Eisai, Celgene; research funding to institute from Astellas, AstraZeneca, Genentech, Novartis, Oncogenex, Roche, Medivation.

CS has served as consultant, participated in advisory boards or received travel grants from AstraZeneca, Byondis B.V., Daiichi Sankyo, Eisai, Exact Sciences, Exeter Pharma, F. Hoffmann-La Roche Ltd, MediTech, Merck Sharp & Dohme, Novartis, Pfizer, Philips, Pierre Fabre, PintPharma, Puma Biotechnology, Sanofi-Aventis, SeaGen, Zymeworks.

TS reports receipt of honoraria for advisory board participation for Roche, Pfizer.

SMT reports receipt of institutional research funding from AstraZeneca, Lilly, Merck, Nektar, Novartis, Pfizer, Genentech/Roche, Immunomedics/Gilead, Exelixis, Bristol-Myers Squibb, Eisai, Nanostring, Cyclacel, Odonate, Seattle Genetics; has served as an advisor/consultant (compensated) for AstraZeneca, Eli Lilly, Merck, Nektar, Novartis, Pfizer, Genentech/Roche, Immunomedics/ Gilead, Bristol-Myers Squibb, Eisai, Nanostring, Puma, Sanofi, Puma, Silverback Therapeutics, G1 Therapeutics, Athenex, OncoPep, Kyowa Kirin Pharmaceuticals, Daiichi-Sankyo, Ellipsis, Infinity, 4D Pharma, Samsung Bioepsis Inc., Chugai Pharmaceuticals, BeyondSpring Pharmaceuticals, OncXerna, OncoSec Medical Incorporated, Certara, Mersana Therapeutics, CytomX, Seattle Genetics.

NCT reports receipt of advisory board honoraria from Astra Zeneca, Bristol-Myers Squibb, Lilly, Merck Sharpe and Dohme, Novartis, Pfizer, Roche/Genentech, GlaxoSmithKline, Zentalis pharmaceuticals, Repare therapeutics, Arvinas; research

funding from Astra Zeneca, BioRad, Pfizer, Roche/Genentech, Merck Sharpe and Dohme, Guardant Health, Invitae, Inivata, Personalis, Natera.

REFERENCES

1. Gao JJ, Cheng J, Bloomquist E, et al. CDK4/6 inhibitor treatment for patients with hormone receptor-positive, HER2-negative, advanced or metastatic breast cancer: a US Food and Drug Administration pooled analysis. *Lancet Oncol.* 2020;21(2):250-260.
2. Schmid P, Adams S, Rugo HS, et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. *N Engl J Med.* 2018;379(22):2108-2121.
3. Swain SM, Miles D, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. *Lancet Oncol.* 2020;21(4):519-530.
4. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med.* 2012;367(19):1783-1791.
5. Bardia A, Hurvitz SA, Tolaney SM, et al. Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer. *N Engl J Med.* 2021;384(16):1529-1541.
6. Murthy RK, Loi S, Okines A, et al. Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. *N Engl J Med.* 2020;382(7):597-609.
7. Cortes J, O'Shaughnessy J, Loesch D, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. *Lancet.* 2011;377(9769):914-923.
8. Gennari A, Stockler M, Puntoni M, et al. Duration of chemotherapy for metastatic breast cancer: a systematic review and meta-analysis of randomized clinical trials. *J Clin Oncol.* 2011;29(16):2144-2149.
9. Biganzoli L, Battisti NML, Wildiers H, et al. Updated recommendations regarding the management of older patients with breast cancer: a joint paper from the European Society of Breast Cancer Specialists (EUSOMA) and the

International Society of Geriatric Oncology (SIOG). *Lancet Oncol.* 2021;22(7):e327-e340.

10. Tabernero J, Vyas M, Giuliani R, et al. Biosimilars: a position paper of the European Society for Medical Oncology, with particular reference to oncology prescribers. *ESMO Open.* 2016;1(6):e000142.
11. Dafni U, Tsourti Z, Alatsathianos I. Breast Cancer Statistics in the European Union: Incidence and Survival across European Countries. *Breast Care (Basel).* 2019;14(6):344-353.
12. Wojtyla C, Bertuccio P, Wojtyla A, et al. European trends in breast cancer mortality, 1980-2017 and predictions to 2025. *Eur J Cancer.* 2021;152:4-17.
13. Allemani C, Matsuda T, Di Carlo V, et al. Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. *Lancet.* 2018;391(10125):1023-1075.
14. Malmgren JA, Mayer M, Atwood MK, et al. Differential presentation and survival of de novo and recurrent metastatic breast cancer over time: 1990-2010. *Breast Cancer Res Treat.* 2018;167(2):579-590.
15. Hölzel D, Eckel R, Bauerfeind I, et al. Improved systemic treatment for early breast cancer improves cure rates, modifies metastatic pattern and shortens post-metastatic survival: 35-year results from the Munich Cancer Registry. *J Cancer Res Clin Oncol.* 2017;143(9):1701-1712.
16. Van Poznak C, Somerfield MR, Bast RC, et al. Use of Biomarkers to Guide Decisions on Systemic Therapy for Women With Metastatic Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol.* 2015;33(24):2695-2704.
17. Cristofanilli M, Turner NC, Bondarenko I, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. *Lancet Oncol.* 2016;17(4):425-439.
18. Cardoso F, Paluch-Shimon S, Senkus E, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). *Ann Oncol.* 2020;31(12):1623-1649.

19. Lee CI, Gold LS, Nelson HD, et al. Comparative effectiveness of imaging modalities to determine metastatic breast cancer treatment response. *Breast.* 2015;24(1):3-11.
20. Accordino MK, Wright JD, Vasan S, et al. Use and Costs of Disease Monitoring in Women With Metastatic Breast Cancer. *J Clin Oncol.* 2016;34(24):2820-2826.
21. Kosmin M, Padhani AR, Gogbashian A, et al. Comparison of Whole-Body MRI, CT, and Bone Scintigraphy for Response Evaluation of Cancer Therapeutics in Metastatic Breast Cancer to Bone. *Radiology.* 2020;297(3):622-629.
22. Fourney DR, Frangou EM, Ryken TC, et al. Spinal instability neoplastic score: an analysis of reliability and validity from the spine oncology study group. *J Clin Oncol.* 2011;29(22):3072-3077.
23. Komorowski AS, Warner E, MacKay HJ, et al. Incidence of Brain Metastases in Nonmetastatic and Metastatic Breast Cancer: Is There a Role for Screening? *Clin Breast Cancer.* 2020;20(1):e54-e64.
24. Cardoso F, Costa A, Norton L, et al. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). *Breast.* 2014;23(5):489-502.
25. Finn RS, Martin M, Rugo HS, et al. Palbociclib and letrozole in advanced breast cancer. *N Engl J Med.* 2016;375(20):1925-1936.
26. Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. *N Engl J Med.* 2016;375(18):1738-1748.
27. Im SA, Lu YS, Bardia A, et al. Overall survival with ribociclib plus endocrine therapy in breast cancer. *N Engl J Med.* 2019;381(4):307-316.
28. Slamon DJ, Neven P, Chia S, et al. Overall survival with ribociclib plus fulvestrant in advanced breast cancer. *N Engl J Med.* 2020;382(6):514-524.
29. Tripathy D, Im SA, Colleoni M, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. *Lancet Oncol.* 2018;19(7):904-915.
30. Goetz MP, Toi M, Campone M, et al. MONARCH 3: Abemaciclib as initial therapy for advanced breast cancer. *J Clin Oncol.* 2017;35(32):3638-3646.

31. Hortobagyi GN, Stemmer SM, III HAB, et al. LBA17_PR - Overall survival (OS) results from the phase III MONALEESA-2 (ML-2) trial of postmenopausal patients (pts) with hormone receptor positive/human epidermal growth factor receptor 2 negative (HR+/HER2−) advanced breast cancer (ABC) treated with endocrine therapy (ET) ± ribociclib (RIB). *Ann Oncol.* 2021;32(suppl_5):S1283-S1346.
32. Martin M, Zielinski C, Ruiz-Borrego M, et al. Palbociclib in combination with endocrine therapy versus capecitabine in hormonal receptor-positive, human epidermal growth factor 2-negative, aromatase inhibitor-resistant metastatic breast cancer: a phase III randomised controlled trial-PEARL. *Ann Oncol.* 2021;32(4):488-499.
33. Park YH, Kim TY, Kim GM, et al. Palbociclib plus exemestane with gonadotropin-releasing hormone agonist versus capecitabine in premenopausal women with hormone receptor-positive, HER2-negative metastatic breast cancer (KCSG-BR15-10): a multicentre, open-label, randomised, phase 2 trial. *Lancet Oncol.* 2019;20(12):1750-1759.
34. Llombart-Cussac A, Pérez-García JM, Bellet M, et al. PARSIFAL: A randomized, multicenter, open-label, phase II trial to evaluate palbociclib in combination with fulvestrant or letrozole in endocrine-sensitive patients with estrogen receptor (ER)[+]/HER2[-] metastatic breast cancer. *Journal of Clinical Oncology.* 2020;38(15_suppl):1007-1007.
35. Dickler MN, Tolaney SM, Rugo HS, et al. MONARCH 1, A Phase II Study of Abemaciclib, a CDK4 and CDK6 Inhibitor, as a Single Agent, in Patients with Refractory HR(+)/HER2(-) Metastatic Breast Cancer. *Clin Cancer Res.* 2017;23(17):5218-5224.
36. André F, Ciruelos E, Rubovszky G, et al. Alpelisib for PIK3CA-mutated, hormone receptor-positive advanced breast cancer. *N Engl J Med.* 2019;380(20):1929-1940.
37. André F, Ciruelos EM, Juric D, et al. Alpelisib plus fulvestrant for PIK3CA-mutated, hormone receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: final overall survival results from SOLAR-1. *Ann Oncol.* 2021;32(2):208-217.
38. Rugo HS, Lerebours F, Ciruelos E, et al. Alpelisib plus fulvestrant in PIK3CA-mutated, hormone receptor-positive advanced breast cancer after a CDK4/6

inhibitor (BYLieve): one cohort of a phase 2, multicentre, open-label, non-comparative study. *Lancet Oncol.* 2021;22(4):489-498.

39. Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *N Engl J Med.* 2012;366(6):520-529.
40. Piccart M, Hortobagyi GN, Campone M, et al. Everolimus plus exemestane for hormone-receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: overall survival results from BOLERO-2†. *Ann Oncol.* 2014;25(12):2357-2362.
41. Cook MM, Al Rabadi L, Kaempf AJ, et al. Everolimus Plus Exemestane Treatment in Patients with Metastatic Hormone Receptor-Positive Breast Cancer Previously Treated with CDK4/6 Inhibitor Therapy. *Oncologist.* 2021;26(2):101-106.
42. Rozenblit M, Mun S, Soulos P, et al. Patterns of treatment with everolimus exemestane in hormone receptor-positive HER2-negative metastatic breast cancer in the era of targeted therapy. *Breast Cancer Res.* 2021;23(1):14.
43. Chandarlapaty S, Chen D, He W, et al. Prevalence of ESR1 Mutations in Cell-Free DNA and Outcomes in Metastatic Breast Cancer: A Secondary Analysis of the BOLERO-2 Clinical Trial. *JAMA Oncol.* 2016;2(10):1310-1315.
44. Rugo HS, Seneviratne L, Beck JT, et al. Prevention of everolimus-related stomatitis in women with hormone receptor-positive, HER2-negative metastatic breast cancer using dexamethasone mouthwash (SWISH): a single-arm, phase 2 trial. *Lancet Oncol.* 2017;18(5):654-662.
45. Jerusalem G, de Boer RH, Hurvitz S, et al. Everolimus Plus Exemestane vs Everolimus or Capecitabine Monotherapy for Estrogen Receptor-Positive, HER2-Negative Advanced Breast Cancer: The BOLERO-6 Randomized Clinical Trial. *JAMA Oncol.* 2018;4(10):1367-1374.
46. Gyawali B, de Vries EGE, Dafni U, et al. Biases in study design, implementation, and data analysis that distort the appraisal of clinical benefit and ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) scoring. *ESMO Open.* 2021;6(3):100117.
47. Robson M, Im SA, Senkus E, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. *N Engl J Med.* 2017;377(6):523-533.

48. Litton JK, Rugo HS, Ettl J, et al. Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. *N Engl J Med.* 2018;379(8):753-763.
49. Gennari A, Bruzzi P, Orlandini C, et al. Activity of first-line epirubicin and paclitaxel in metastatic breast cancer is independent of type of adjuvant therapy. *Br J Cancer.* 2004;90(5):962-967.
50. European Medicines Agency. EMA recommendations on DPD testing prior to treatment with fluorouracil, capecitabine, tegafur and flucytosine Available at https://www.ema.europa.eu/en/news/ema-recommendations-dpd-testing-prior-treatment-fluorouracil-capecitabine-tegafur-flucytosine. Published 2020. Accessed July 1, 2021.
51. Miles DW, Diéras V, Cortés J, et al. First-line bevacizumab in combination with chemotherapy for HER2-negative metastatic breast cancer: pooled and subgroup analyses of data from 2447 patients. *Ann Oncol.* 2013;24(11):2773-2780.
52. Baselga J, Cortes J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med.* 2012;366(2):109-119.
53. Rimawi M, Ferrero JM, de la Haba-Rodriguez J, et al. First-Line Trastuzumab Plus an Aromatase Inhibitor, With or Without Pertuzumab, in Human Epidermal Growth Factor Receptor 2-Positive and Hormone Receptor-Positive Metastatic or Locally Advanced Breast Cancer (PERTAIN): A Randomized, Open-Label Phase II Trial. *J Clin Oncol.* 2018;36(28):2826-2835.
54. Kaufman B, Mackey JR, Clemens MR, et al. Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone receptor-positive metastatic breast cancer: results from the randomized phase III TAnDEM study. *J Clin Oncol.* 2009;27(33):5529-5537.
55. Yuan Z, Huang J-J, Hua Z, et al. Trastuzumab plus endocrine therapy or chemotherapy as first-line treatment for metastatic breast cancer with hormone receptor-positive and HER2-positive: The sysucc-002 randomized clinical trial. *J Clin Oncol.* 2021;39(15_suppl):1003-1003(abstract 1003).
56. Johnston SRD, Hegg R, Im SA, et al. Phase III, Randomized Study of Dual Human Epidermal Growth Factor Receptor 2 (HER2) Blockade With Lapatinib Plus Trastuzumab in Combination With an Aromatase Inhibitor in

Postmenopausal Women With HER2-Positive, Hormone Receptor-Positive Metastatic Breast Cancer: ALTERNATIVE. *J Clin Oncol.* 2018;36(8):741-748.

57. Johnston S, Pippen J, Jr., Pivot X, et al. Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor-positive metastatic breast cancer. *J Clin Oncol.* 2009;27(33):5538-5546.
58. Cortés J, Fumoleau P, Bianchi GV, et al. Pertuzumab monotherapy after trastuzumab-based treatment and subsequent reintroduction of trastuzumab: activity and tolerability in patients with advanced human epidermal growth factor receptor 2-positive breast cancer. *J Clin Oncol.* 2012;30(14):1594-1600.
59. Krop IE, Kim SB, Gonzalez-Martin A, et al. Trastuzumab emtansine versus treatment of physician's choice for pretreated HER2-positive advanced breast cancer (TH3RESA): a randomised, open-label, phase 3 trial. *Lancet Oncol.* 2014;15(7):689-699.
60. Cortés J, Kim S, Chung W, et al. LBA1 - Trastuzumab deruxtecan (T-DXd) vs trastuzumab emtansine (T-DM1) in patients (Pts) with HER2+ metastatic breast cancer (mBC): Results of the randomized phase III DESTINY-Breast03 study. *Ann Oncol.* 2021;32(suppl_5):S1283-S1346.
61. Lin NU, Borges V, Anders C, et al. Intracranial Efficacy and Survival With Tucatinib Plus Trastuzumab and Capecitabine for Previously Treated HER2-Positive Breast Cancer With Brain Metastases in the HER2CLIMB Trial. *J Clin Oncol.* 2020;38(23):2610-2619.
62. Murthy R, Borges VF, Conlin A, et al. Tucatinib with capecitabine and trastuzumab in advanced HER2-positive metastatic breast cancer with and without brain metastases: a non-randomised, open-label, phase 1b study. *Lancet Oncol.* 2018;19(7):880-888.
63. Modi S, Saura C, Yamashita T, et al. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. *N Engl J Med.* 2020;382(7):610-621.
64. Modi S, Saura C, Yamashita T, et al. PD3-06. Updated results from DESTINY-breast01, a phase 2 trial of trastuzumab deruxtecan (T-DXd) in HER2 positive metastatic breast cancer. Paper presented at: San Antonio Breast Cancer Symposium2020.
65. Blackwell KL, Burstein HJ, Storniolo AM, et al. Randomized study of Lapatinib alone or in combination with trastuzumab in women with ErbB2-positive,

trastuzumab-refractory metastatic breast cancer. *J Clin Oncol.* 2010;28(7):1124-1130.

66. Saura C, Oliveira M, Feng YH, et al. Neratinib Plus Capecitabine Versus Lapatinib Plus Capecitabine in HER2-Positive Metastatic Breast Cancer Previously Treated With ≥ 2 HER2-Directed Regimens: Phase III NALA Trial. *J Clin Oncol.* 2020;38(27):3138-3149.
67. Rugo HS, Im SA, Cardoso F, et al. Efficacy of Margetuximab vs Trastuzumab in Patients With Pretreated ERBB2-Positive Advanced Breast Cancer: A Phase 3 Randomized Clinical Trial. *JAMA Oncol.* 2021;7(4):573-584.
68. Foulkes WD, Smith IE, Reis-Filho JS. Triple-negative breast cancer. *N Engl J Med.* 2010;363(20):1938-1948.
69. Cortes J, Cescon DW, Rugo HS, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial. *Lancet.* 2020;396(10265):1817-1828.
70. Schmid P, Rugo HS, Adams S, et al. Atezolizumab plus nab-paclitaxel as first-line treatment for unresectable, locally advanced or metastatic triple-negative breast cancer (IMpassion130): updated efficacy results from a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2020;21(1):44-59.
71. Miles D, Gligorov J, André F, et al. Primary results from IMpassion131, a double-blind, placebo-controlled, randomised phase III trial of first-line paclitaxel with or without atezolizumab for unresectable locally advanced/metastatic triple-negative breast cancer. *Ann Oncol.* 2021;32(8):994-1004.
72. Rugo HS, Cortés J, Cescon DW, et al. LBA16 - KEYNOTE-355: Final results from a randomized, double-blind phase III study of first-line pembrolizumab + chemotherapy vs placebo + chemotherapy for metastatic TNBC. *Ann Oncol.* 2021;32(suppl_5):S1283-S1346.
73. Tutt A, Tovey H, Cheang MCU, et al. Carboplatin in BRCA1/2-mutated and triple-negative breast cancer BRCAness subgroups: the TNT Trial. *Nat Med.* 2018;24(5):628-637.

74. Piccart-Gebhart MJ, Burzykowski T, Buyse M, et al. Taxanes alone or in combination with anthracyclines as first-line therapy of patients with metastatic breast cancer. *J Clin Oncol.* 2008;26(12):1980-1986.
75. Yardley DA, Coleman R, Conte P, et al. nab-Paclitaxel plus carboplatin or gemcitabine versus gemcitabine plus carboplatin as first-line treatment of patients with triple-negative metastatic breast cancer: results from the tnAcity trial. *Ann Oncol.* 2018;29(8):1763-1770.
76. Carrick S, Parker S, Wilcken N, et al. Single agent versus combination chemotherapy for metastatic breast cancer. *Cochrane Database Syst Rev.* 2005(2):Cd003372.
77. Bardia A, Messersmith WA, Kio EA, et al. Sacituzumab govitecan, a Trop-2-directed antibody-drug conjugate, for patients with epithelial cancer: final safety and efficacy results from the phase I/II IMMU-132-01 basket trial. *Ann Oncol.* 2021;32(6):746-756.
78. Hurvitz SA, Tolaney SM, Punie K, et al. GS3-06. Biomarker evaluation in the phase 3 ASCENT study of sacituzumab govitecan versus chemotherapy in patients with metastatic triple-negative breast cancer. Paper presented at: San Antonio Breast Cancer Symposium2020; Virtual Meeting.
79. Winer EP, Lipatov O, Im SA, et al. Pembrolizumab versus investigator-choice chemotherapy for metastatic triple-negative breast cancer (KEYNOTE-119): a randomised, open-label, phase 3 trial. *Lancet Oncol.* 2021;22(4):499-511.
80. Bachelot T, Filleron T, Bieche I, et al. Durvalumab compared to maintenance chemotherapy in metastatic breast cancer: the randomized phase II SAFIR02-BREAST IMMUNO trial. *Nat Med.* 2021;27(2):250-255.
81. Robson ME, Tung N, Conte P, et al. OlympiAD final overall survival and tolerability results: Olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer. *Ann Oncol.* 2019;30(4):558-566.
82. Diéras V, Han HS, Kaufman B, et al. Veliparib with carboplatin and paclitaxel in BRCA-mutated advanced breast cancer (BROCADE3): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2020;21(10):1269-1282.
83. Robson M, Ruddy KJ, Im SA, et al. Patient-reported outcomes in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer

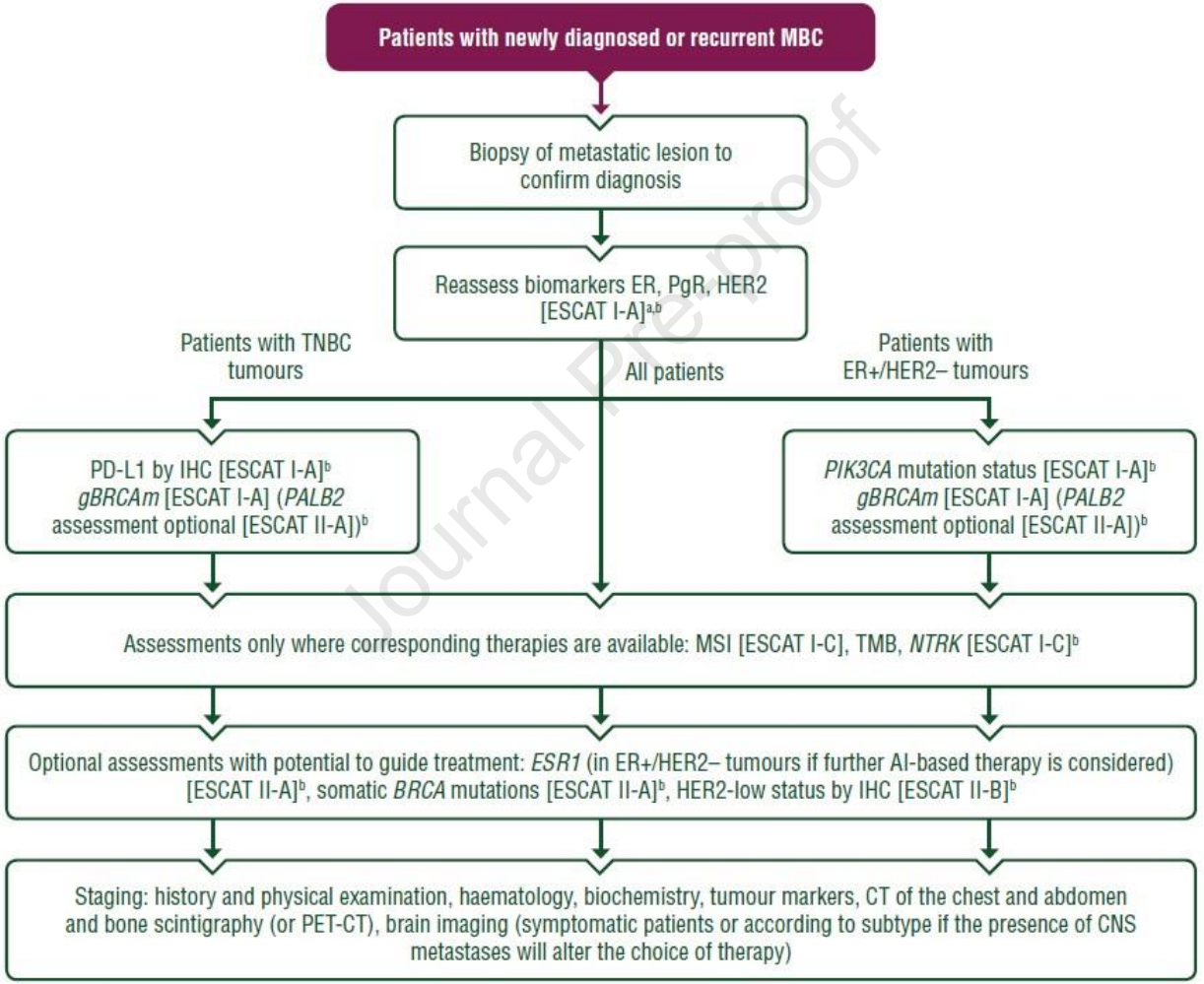
receiving olaparib versus chemotherapy in the OlympiAD trial. *Eur J Cancer.* 2019;120:20-30.

84. Ettl J, Quek RGW, Lee KH, et al. Quality of life with talazoparib versus physician's choice of chemotherapy in patients with advanced breast cancer and germline BRCA1/2 mutation: patient-reported outcomes from the EMBRACA phase III trial. *Ann Oncol.* 2018;29(9):1939-1947.
85. Guckenberger M, Lievens Y, Bouma AB, et al. Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation. *Lancet Oncol.* 2020;21(1):e18-e28.
86. Coleman R, Hadji P, Body JJ, et al. Bone health in cancer: ESMO Clinical Practice Guidelines. *Ann Oncol.* 2020;31(12):1650-1663.
87. Le Rhun E, Guckenberger M, Smits M, et al. EANO-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with brain metastasis from solid tumours. *Ann Oncol.* 2021.
88. Le Rhun E, Weller M, Brandsma D, et al. EANO-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with leptomeningeal metastasis from solid tumours. *Ann Oncol.* 2017;28(suppl_4):iv84-iv99.
89. Mateo J, Chakravarty D, Dienstmann R, et al. A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT). *Ann Oncol.* 2018;29(9):1895-1902.
90. ESMO Clinical Practice Guidelines: supportive and palliative care. Available at https://www.esmo.org/guidelines/supportive-and-palliative-care. Accessed June 16, 2021.
91. Turner-Bowker DM, Hao Y, Foley C, et al. The use of patient-reported outcomes in advanced breast cancer clinical trials: a review of the published literature. *Curr Med Res Opin.* 2016;32(10):1709-1717.
92. Caswell-Jin JL, Plevritis SK, Tian L, et al. Change in Survival in Metastatic Breast Cancer with Treatment Advances: Meta-Analysis and Systematic Review. *JNCI Cancer Spectr.* 2018;2(4):pky062.
93. Cherny NI, Dafni U, Bogaerts J, et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Ann Oncol.* 2017;28(10):2340-2366.

94. Dykewicz CA. Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. *Clin Infect Dis.* 2001;33(2):139-144 (adapted from: Gross PA, Barrett TL, Dellinger EP, et al. Purpose of quality standards for infectious diseases. *Clin Infect Dis*.1994;1918:1421).

Figures

Figure 1. Diagnostic work-up and staging of MBC



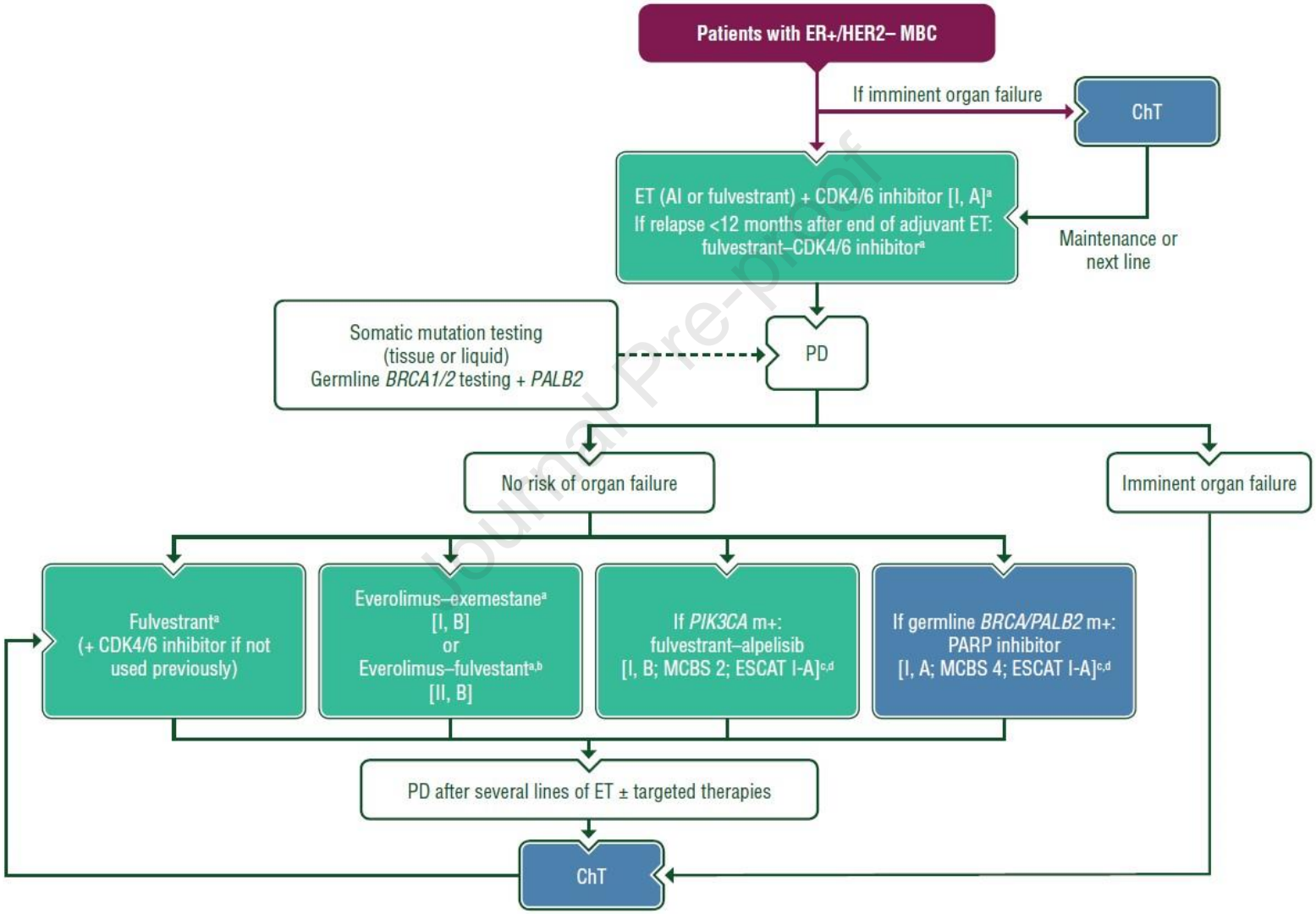
Purple: general categories or stratification; white: other aspects of management.

AI, aromatase inhibitor; CNS, central nervous system; CT, computed tomography; ER, oestrogen receptor; ESCAT, ESMO scale for clinical actionability of molecular targets; ESR1, oestrogen receptor 1; *gBRCAm*, germline *BRCA1/2* mutation; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; MBC, metastatic breast cancer; MSI, microsatellite instability; NTRK, neurotrophic tyrosine receptor kinase; PALB2, partner and localiser of BRCA2; PD-L1, programmed death-ligand 1; PET, positron emission tomography; PgR, progesterone receptor; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; TMB, tumour mutation burden; TNBC, triple-negative breast cancer.

[a] If there are important differences in ER/PgR and HER2 status between the primary tumour and recurrence, patients should be managed according to receptor status of the recurrent disease biopsy.

[b] ESCAT scores apply to genomic alterations only. These scores have been defined by the guideline authors and validated by the ESMO Translational Research and Precision Medicine Working Group.[89]

Figure 2. Treatment of ER-positive/HER2-negative MBC



Purple: general categories or stratification; turquoise: combination of treatments or other systemic treatments; white: other aspects of management; blue: systemic anticancer therapy.

AI, aromatase inhibitor; ChT, chemotherapy; EMA, European Medicines Agency; ER, oestrogen receptor; ESCAT, ESMO scale for clinical actionability of molecular targets; ESMO-MCBS, European Society for Medical Oncology-Magnitude of Clinical Benefit Scale; ESR1, oestrogen receptor 1; ET, endocrine therapy; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; m, mutation; MBC, metastatic breast cancer; OFS, ovarian function suppression; PALB2, partner and localiser of BRCA2; PARP, poly (ADP-ribose) polymerase; PD, progressive disease; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

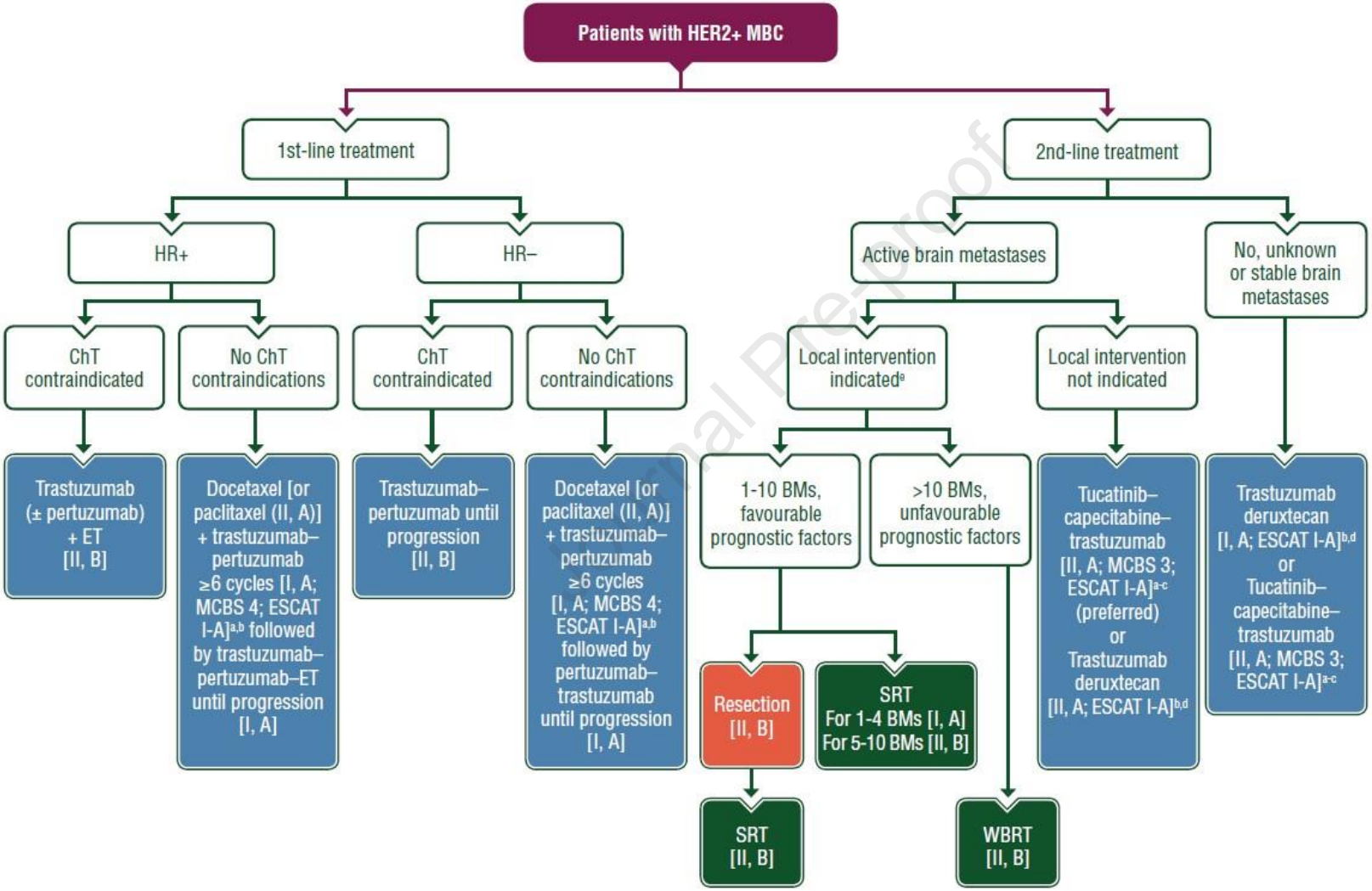
[a] OFS if the patient is premenopausal.

[b] Preferred if the patient is *ESR1* mutation positive [ESCAT score: II-A].[d]

[c] ESMO-MCBS version 1.1[93] was used to calculate scores for new therapies/indications approved by the EMA or FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/scale-evaluation-forms-v1.0-v1.1/scale-evaluation-forms-v1.1).

[d] ESCAT scores apply to genomic alterations only. These scores have been defined by the guideline authors and validated by the ESMO Translational Research and Precision Medicine Working Group.[89]

Figure 3. First- and second-line treatment of HER2-positive MBC



Purple: general categories or stratification; red: surgery; turquoise: combination of treatments or other systemic treatments; green: RT; white: other aspects of management; blue: systemic anticancer therapy.

BM, brain metastasis; ChT, chemotherapy; CNS, central nervous system; EMA, European Medicines Agency; ESCAT, ESMO scale for clinical actionability of molecular targets; ESMO-MCBS, European Society for Medical Oncology-Magnitude of Clinical Benefit Scale; ET, endocrine therapy; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MBC, metastatic breast cancer; PD, progressive disease; RT, radiotherapy; SRT, stereotactic radiotherapy; T-DM1, ado-trastuzumab emtansine; WBRT, whole brain radiotherapy.

[a] ESMO-MCBS version 1.1[93] was used to calculate scores for new therapies/indications approved by the EMA or FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/scale-evaluation-forms-v1.0-v1.1/scale-evaluation-forms-v1.1).

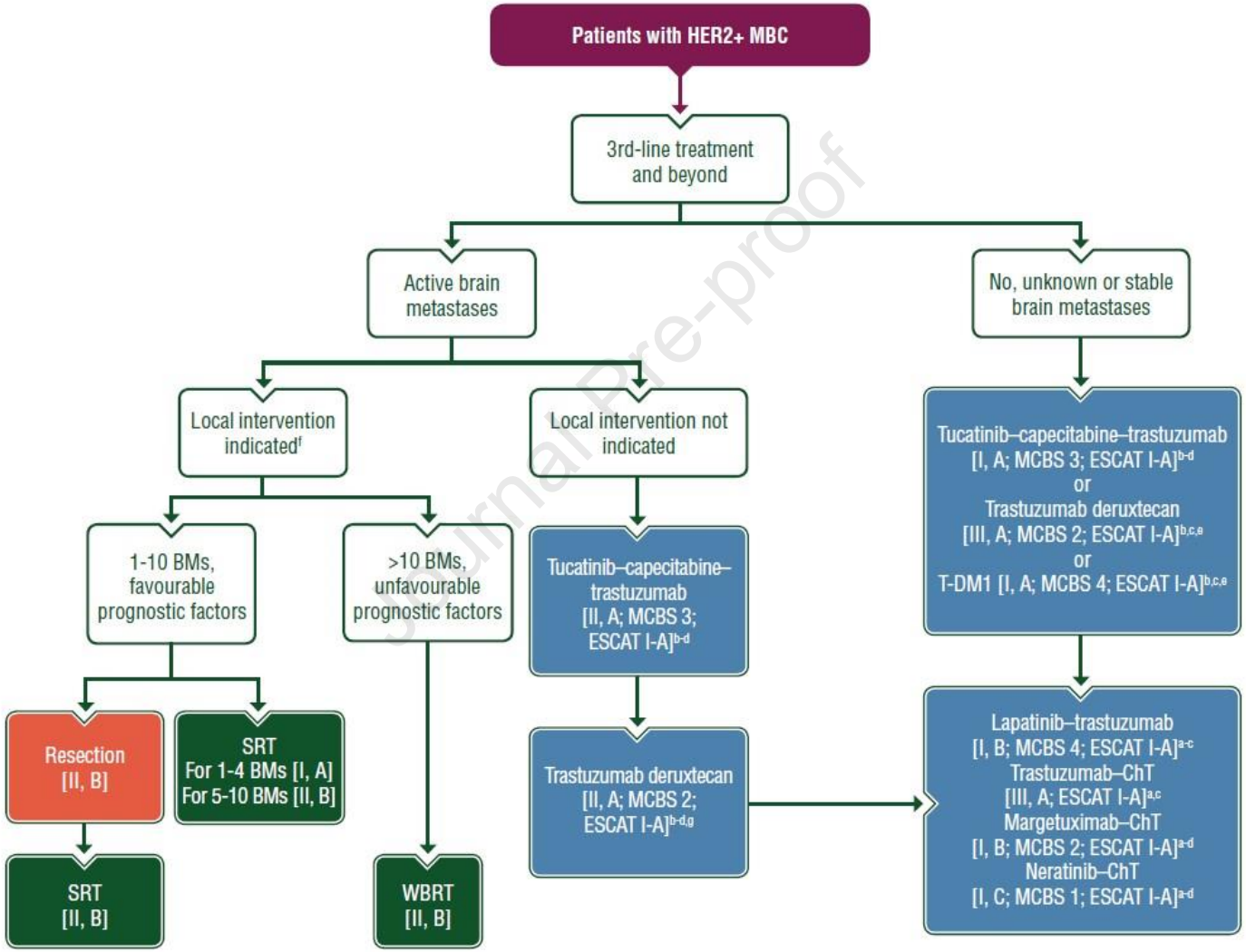
[b] ESCAT scores apply to genomic alterations only. These scores have been defined by the guideline authors and validated by the ESMO Translational Research and Precision Medicine Working Group.[89]

[c] FDA-approved, not EMA-approved.

[d] Not FDA-approved for use in second line.

[e] Keep on current systemic therapy unless PD outside CNS.

Figure 4. Third-line and beyond treatment of HER2-positive MBC



Purple: general categories or stratification; red: surgery; turquoise: combination of treatments or other systemic treatments; green: RT; white: other aspects of management; blue: systemic anticancer therapy.

BM, brain metastasis; ChT, chemotherapy; CNS, central nervous system; EMA, European Medicines Agency; ESCAT, ESMO scale for clinical actionability of molecular targets; ESMO-MCBS, European Society for Medical Oncology-Magnitude of Clinical Benefit Scale; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer; PD, progressive disease; RT, radiotherapy; SRT, stereotactic radiotherapy; T-DM1, ado-trastuzumab emtansine; WBRT, whole brain radiotherapy.

[a] There are no data for any of these combinations after tucatinib- and/or trastuzumab deruxtecan-based therapy.

[b] ESMO-MCBS version 1.1[93] was used to calculate scores for new therapies/indications approved by the EMA or FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/scale-evaluation-forms-v1.0-v1.1/scale-evaluation-forms-v1.1).

[c] ESCAT scores apply to genomic alterations only. These scores have been defined by the guideline authors and validated by the ESMO Translational Research and Precision Medicine Working Group.[89]

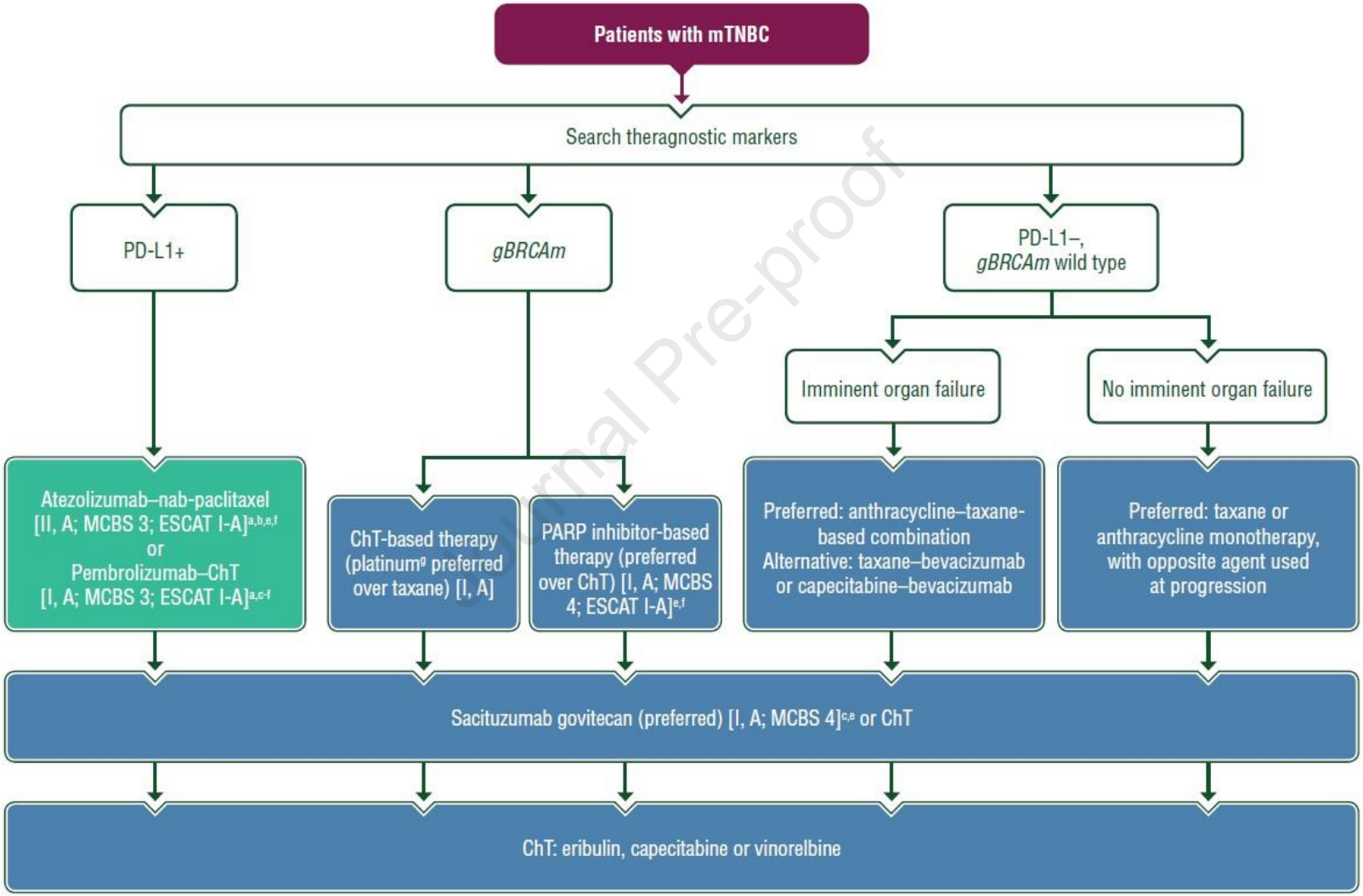
[d] FDA-approved, not EMA-approved.

[e] If not received as second-line therapy.

[f] Keep on current systemic therapy unless PD outside CNS.

[g] If not previously used, including all other drugs that are also a second-line treatment option.

Figure 5. Treatment of mTNBC



Purple: general categories or stratification; turquoise: combination of treatments or other systemic treatments; green: RT; white: other aspects of management; blue: systemic anticancer therapy.

ChT, chemotherapy; EMA, European Medicines Agency; ESCAT, ESMO scale for clinical actionability of molecular targets; ESMO-MCBS, European Society for Medical Oncology-Magnitude of Clinical Benefit Scale; FDA, Food and Drug Administration; *gBRCAm*, germline *BRCA1/2* mutation; ICI, immune checkpoint inhibitor; mTNBC, metastatic triple-negative breast cancer; PARP, poly (ADP-ribose) polymerase; PD-L1, programmed death-ligand 1.

[a] May be considered as monotherapy in further lines in case of high PD-L1 positivity and no previous exposure to ICI.

[b] EMA-approved, not FDA-approved.

[c] FDA-approved, not EMA-approved.

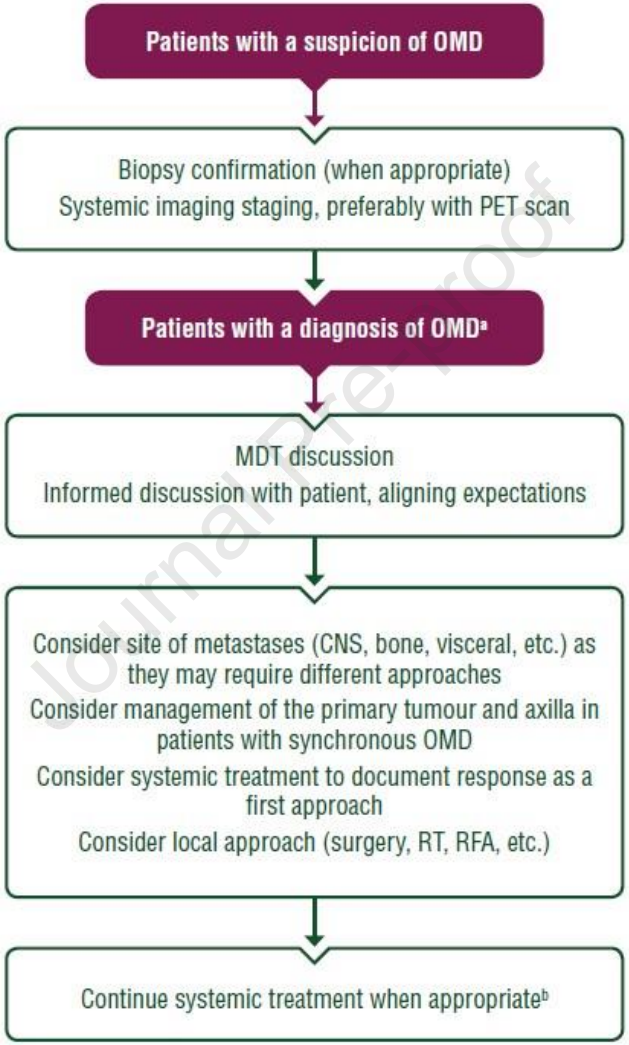
[d] ChT physician's choice of nab-paclitaxel, paclitaxel or gemcitabine/carboplatin.

[e] ESMO-MCBS version 1.1[93] was used to calculate scores for new therapies/indications approved by the EMA or FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/scale-evaluation-forms-v1.0-v1.1/scale-evaluation-forms-v1.1).

[f] ESCAT scores apply to genomic alterations only. These scores have been defined by the guideline authors and validated by the ESMO Translational Research and Precision Medicine Working Group.[89]

[g] If not used previously.

Figure 6. Treatment of OMD



Purple: general categories or stratification; white: other aspects of management.

CNS, central nervous system; MDT, multidisciplinary team; OMD, oligometastatic disease; PET, positron emission tomography; RFA, radiofrequency ablation; RT, radiotherapy.

[a] Consider elements in current definitions, i.e. limited or low-volume metastatic disease; up to 5 lesions in total, not necessarily in the same organ; all potentially amenable to receive local treatment.

[b] The duration of systemic treatment remains a topic of debate.